FDA Executive Summary

P100026

NeuroPace

RNS® System for Epilepsy

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1. Introduction

This is FDA's Executive Summary of premarket approval (PMA) application P100026 from NeuroPace, Inc. for the NeuroPace RNS® System for the treatment of partial onset seizures. This summary contains a brief device description and a summary of the feasibility and pivotal clinical studies conducted by the sponsor. The sponsor bases its request for approval of the NeuroPace RNS® System on the results of the pivotal study data and feasibility safety data (which is summarized in this document), preclinical bench and animal testing, and manufacturing controls. The Panel will be asked to comment on specific aspects of the pivotal study and related materials that are highlighted in this summary. .

2. Device Description

The RNS® System Neurostimulator is surgically implanted subcutaneously in the cranium. The Neurostimulator senses and records electrocorticographic (ECoG) patterns from intracranial electrodes and delivers short trains of current pulses to the brain that are intended to interrupt the ECoG ictal discharge. Depth and/or Cortical Strip leads, each with four electrode contacts, are provided for use with the RNS® System Neurostimulator. The Neurostimulator can accommodate up to two leads. Electrode placement is based on a localization performed previously as part of a pre-surgical evaluation.

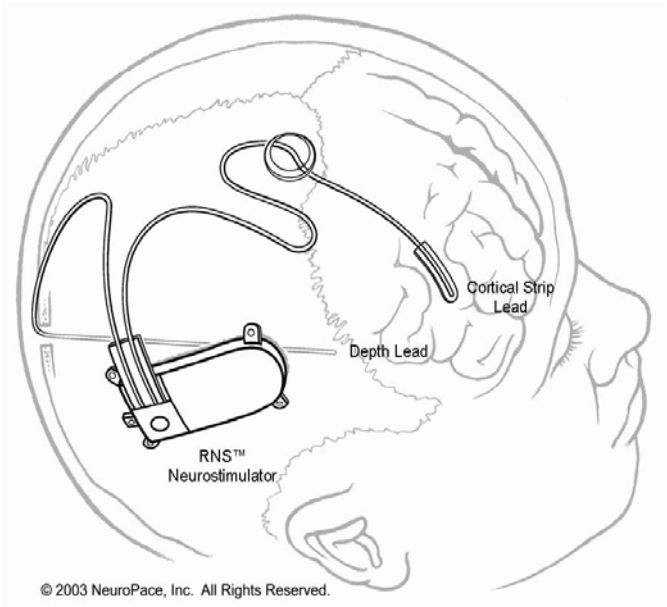


Figure 1. RNS® System Implanted Components

The Neurostimulator detection and stimulation parameters are non-invasively adjusted with the goal of optimizing control of epileptic seizures and for controlling stimulation-related side effects. The adjustments are made utilizing short-range wireless radiofrequency communication using the NeuroPace® Programmer (model PGM-300). The Neurostimulator can be programmed using a wide range of different detection algorithms and responsive stimulation outputs.

2.1. Electrographic Sensing and Storage

The RNS® System Neurostimulator detection algorithm continuously monitors electrographic activity through the Depth and Cortical Strip electrodes. The ECoG data are continually recorded, but only the ECoG data immediately before and after a storage trigger event are retained for review by the physician and periodically uploaded to the sponsor database. Storage of ECoG data can be programmed to be triggered by the detection of a specific event (such as abnormal electrical activity), responsive stimulation, by the time of day, or by a magnet swipe. (An RNS® System magnet is provided to the patient and can be used to indicate a clinical event has occurred and trigger storage of ECoG data.) The physician is able to view ECoG recordings and can assess the correlation of detections with reported clinical seizures and the effects of stimulation on the ECoG.

2.2. Detection Algorithms

Three detection tools (area, line-length, and bandpass) are provided. The detection tools are configurable and can be adjusted by the physician to optimize the detection for each individual patient. Up to two independent detectors can be programmed for any two sensing channels. The bandpass tool is used to detect spikes and rhythmic activity occurring in specific frequency ranges. The line length algorithm is used to identify changes in both amplitude and frequency. The area feature is used to identify changes in overall signal energy without regard to frequency.

Modifying the configuration by adjusting the detection tools impacts the sensitivity and specificity of the detection algorithm. Note that the feasibility and pivotal trials (summarized in this document and performed under IDE G010126) were not designed to assess the accuracy of the detection algorithm for detecting epileptiform activity or seizures, but rather were designed to assess the safety and effectiveness of the RNS® System as a whole.

During the IDE review, the detection algorithm was not fully evaluated for its efficacy in accurately identifying epileptiform activity and seizures. Rather verification and validation testing provided for the detection algorithm were determined by the FDA to be adequate for proceeding with the IDE feasibility and pivotal studies (i.e., the risks to the subjects for participating in the studies were not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained). Testing of the detection algorithm included the following:

- [redacted]
- [redacted]

- [redacted]
- [redacted]

2.3. Responsive Stimulation

The Neurostimulator delivers constant current, charge balanced pulses, and has a number of programmable output settings including pulse duration per phase, output current, and pulse repetition rate. The Neurostimulator can be programmed to deliver up to five individually configured sequential stimulation therapies upon detection of an ictal ECoG pattern, where each therapy is composed of two independently configurable bursts. After each therapy is delivered, stimulation is disabled, and the Neurostimulator attempts to re-detect the programmed ECoG pattern. The duration over which this happens is programmed by the user. Following this interval, if the ECoG pattern is still detected using the same detection algorithm, the next (sequential) therapy will be delivered. If the ECoG pattern is no longer detected, the remaining stimulations will not be delivered and the episode ends. The stimulation therapy sequence will refresh with the detection of each new episode.

Each of the five stimulation therapies in the therapy sequence may be comprised of one or two bursts. The first stimulation therapy in the therapy sequence may be configured in one of two ways:

- Different bursts may be delivered in response to a specific event detector (Pattern A or Pattern B); or
- Up to two bursts may be selected to be delivered in response to either event detector.

Additional responsive stimulation therapy sequence settings include:

- Post-episode monitoring interval: this specifies the time during which the Neurostimulator will disable therapies after detecting the end of an episode;
- Stimulation therapy limit per day: this specifies the maximum number of stimulations that can be delivered over 24 hours before the Neurostimulator disables therapy;
- Adaptive pulse interval settings: these optional settings specify the frequency of the first stimulation burst in a therapy according to the frequency of the ECoG signal sensed by the Neurostimulator; and
- Synchronization settings: these optional settings specify that the first pulse in a burst is delivered synchronous to peaks in the sensed ECoG signal.

The initial recommended stimulation settings were a frequency of 200 Hz, a pulse duration of 160 µs, and a 100 ms burst duration (Table 18). Instructions for making subsequent changes to detection and stimulation parameters were not specified in the protocol. However, stimulation settings could be modified by the investigator based on subject status (e.g., seizure recurrence), subject perception of stimulation (for the Treatment group) and the presence of after discharges. Section 7.4 below describes the range of stimulus parameters used in the IDE. .

An example of sequential detection and stimulation is shown in Figure 2 below. In this example, stimulation parameters are programmed to vary from Burst 1 to Burst 2 (Therapy 1) and stimulation after re-detection (Therapy 2). If the epileptiform activity is no longer detected, the remaining therapies will not be delivered and the episode ends. The therapy sequence will refresh with the detection of each new episode.

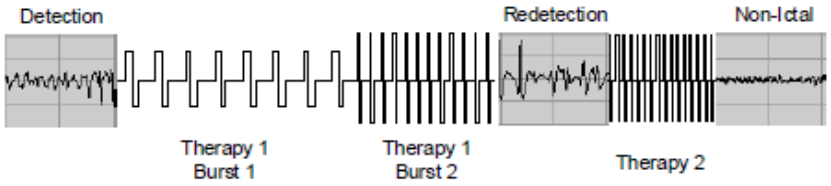


Figure 2. Example of Sequential Detection and Stimulation

2.4. RNS® System Safety Controls

The RNS® System has controls that keep current densities below 25 µC/cm2/phase. The physician may decide that the detection is adequate or may decide to re-program the Neurostimulator so that the detection occurs earlier or later in the discharge.

3. Proposed Indications for Use

The sponsor proposes the following Indications for Use:

"The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications."

The Panel will be asked to consider the proposed indications for use and discuss whether they are supported by the data in the PMA.

4. Regulatory History

NeuroPace conducted feasibility and pivotal trials under IDE G030126. When the PMA was initially submitted, the sponsor did not provide 12 month follow-up data on all study subjects (as requested by the FDA in the IDE), so the data were not accepted for review. A letter informing the sponsor of this "Not Filing" decision was issued on July 26, 2010. The PMA was filed on November 9, 2010 following submission of an amendment with 12 month data on all subjects. FDA issued a Major Deficiency letter on June 14, 2011, seeking clarification on clinical and statistical issues. The sponsor provided additional

information, and FDA is now seeking scientific and clinical input from the Neurological Devices Panel on whether the data in the submission provide a reasonable assurance of the safety and effectiveness of the RNS® System for its intended use.

As of the writing of this Summary, the IDE remains open and all subjects continue to be followed.

5. Overview of Epilepsy

The term epilepsy is a general term for an "enduring predisposition" (Guidelines for epidemiologic studies on epilepsy, 1993) to unprovoked epileptic seizures. Epileptic seizures represent the clinical manifestations of an underlying abnormality in the brain. The abnormality responsible for initiating the seizures can vary from specific genetically determined neuronal ion channel disorders to focal structural abnormalities such as cortical dysplasia, stroke and tumors. The underlying pathophysiology of an epileptic seizure is thought to involve an "excessive neuronal discharge" that is typically manifested on electroencephalographic (EEG) recordings as a hypersynchronous, high frequency pattern of activity that may begin locally but subsequently spread more generally or the discharge may appear to be generalized from the beginning.

The causes of epilepsy vary by age group. Familial or genetic causes are more commonly seen in the younger age groups and structural causes such as head trauma, stroke and tumors are more commonly seen in the older age groups. Primary generalized seizures such as absence seizures (for which the term "petit mal" had been used) or primary generalized epilepsies such as juvenile myoclonic epilepsy are more typically seen in the younger age groups whereas partial seizures are seen in all age groups but are the predominant seizure type in adults.

The clinical features of an epileptic seizure are typically classified based on whether the onset is localized, resulting in a "focal" or "partial seizure" or not localized resulting in a "generalized" seizure. Generalized seizures may have been generalized from the onset, i.e. a "primary generalized seizure", or evolve from a focal onset seizure, i.e. a "secondarily generalized seizure". Focal/partial seizures may be associated with no impairment of cognition or awareness, for which the term "simple partial" seizure has been used or there may be associated impairment in awareness and/or cognition for which the term "complex partial seizure" has been used. The specific manifestations of a simple partial seizure are representative of the area of origin. Examples include partial seizures with sensory, motor, autonomic or psychic manifestations. Non-epileptic seizure-like events occur in a variety of circumstances and must be distinguished from epileptic seizures, if necessary by video EEG monitoring. The terms "psychogenic" seizures or "pseudoseizures" may be used for these events although these terms imply underlying dynamics that not consistently present. Patients with these events are typically excluded from trials of treatment for epilepsy. The term "status epilepticus" is used to describe prolonged seizures or repeated seizures without adequate recovery between the individual seizures.

The most common example of a complex partial seizure is that originating in the mesial temporal region. This type of partial seizure typically begins with simple partial manifestations commonly known as an "aura" consisting of phenomena such as an intense feeling of experiencing something strangely familiar ("déjà vu) or an olfactory or visual hallucination. During the complex partial seizure patients typically manifest stereotyped behaviors known as automatisms such as repetitive swallowing, lip smacking or more complex behaviors such as stereotyped vocalizations. During this period, although patients may

appear somewhat purposeful, they in fact are unaware and have no recollection of the events during this phase of the seizure.

Complex partial seizures originating in areas other than the temporal region, i.e. “extra-temporal”, differ significantly from those of temporal origin. The frontal lobe is the most common locus for this type of complex partial seizure which tends to occur in clusters, often many times per day. A simple partial onset or “aura” is not as typical of complex partial seizures of extra-temporal origin. Although the behavioral manifestations are stereotyped they tend to be more bizarre such that an erroneous diagnosis of non-epileptic events may be made. While complex partial seizures of mesial temporal origin have fairly typical clinical manifestations and are often associated with structural changes in mesial temporal structures in imaging studies, those of extra-temporal origin are more variable in their clinical manifestations and are not as commonly associated with recognizable pathology on imaging. Simple partial seizures with disabling motor manifestations, complex partial seizures of both temporal and extra-temporal origin and secondarily generalized seizures were the types of seizures included in the studies of the device under discussion at this panel meeting.

The goal of any treatment for seizures is complete seizure freedom without adverse effects of the prescribed treatment(s). In the absence of achieving this goal patients will be unable to drive a car, most will be limited in employment opportunities and all are likely to endure both social and psychological consequences. For many people even one seizure a year can be disabling. The first option is usually pharmacologic treatment. There are a number of drugs approved for the treatment of partial seizures with or without secondary generalization. Approximately 50-60% of adult patients achieve sustained seizure freedom sustained for at least one year with the first prescribed anti-seizure drug (Kwan P, 2000) and approximately 20-30% of those resistant to the first drug will achieve sustained seizure freedom on an alternate monotherapy (Kwan P, 2000; Schiller Y, 2008; Stephen LJ, 2002). However successive trials of alternate drugs as monotherapy or combinations of two or more anti-seizure medications result in rapidly diminishing success rates for the overall population. Most studies report a very small chance of achieving seizure freedom after several trials of monotherapy and/or combination therapy. One recent study did report that there may be up to 10-20% chance of achieving seizure freedom in groups of patients attempting new regimens after three had already failed (Stephen LJ, 2002 and Luciano and Shorvon, 2007). If seizure freedom cannot be achieved then a meaningful reduction in seizure frequency, especially for complex partial and generalized seizures may be helpful. A 50% reduction in the frequency of seizures is typically considered a meaningful measure of patient level success in patients for whom seizure freedom has not been achieved (Ben-Menachem et al., 2010 and Costa, et al., 2011). In this refractory population controlled trials of anti-seizure medications approved as adjunctive treatment of partial seizures with or without secondary generalization the 50% responder rate has been approximately 20% (Beyenburg et al., 2010). It should be noted these responder rates are typically accompanied by a statistically significant reduction in the median percent reduction in seizure frequency. A treatment effect measured with other endpoints or analysis methods cannot necessarily be compared to the treatment effects seen in these drug trials.

Many of these medicines, especially when used in combination, are associated with significant adverse effects, especially cognitive deficits. These adverse effects can be especially problematic in vulnerable populations such as young patients still in school, those with jobs requiring cognitive skills, those operating dangerous equipment, or the elderly already on multiple drugs. In addition, the use of several of the anti-seizure drugs is limited in women of child bearing potential both because the drugs have been

associated with fetal malformations and because they alter levels of hormonal contraceptives. Short and long-term enzyme induction may pose other health hazards such as osteoporosis and interference with the effectiveness of medications for other medical conditions (Brodie, Mintzer, et al., 2012).

With the use of alternate drugs or combinations of more than one drug up to 70% of adult patients with partial seizures may achieve sustained seizure freedom (Brodie, Barry, et al., 2012). Given the overall incidence of epilepsy (0.5 to 1.0% of the US population), this leaves a large number of patients who do not achieve adequate seizure control without significant adverse effects while being treated with currently available medications. A relative minority of these patients may be candidates for resective surgery if the clinical features of the seizures, interictal and ictal EEG, imaging data along with ancillary studies are concordant in localizing the source of the seizures to a resectable focus. Approximately 70% of patients properly selected for mesial temporal resection achieve seizure free status (Engel et al., 2012 and Wiebe et al., 2001). Seizure freedom is typically achieved in 60% or less for resection of foci outside the mesial temporal region and is particularly low for those without a detectable lesion on imaging studies (Elsharkawy et al., 2008; Jeha, et al., 2007; Smith et al., 1997). For some patients the use of vagal nerve stimulation is an option. VNS achieves seizure freedom in relatively few patients and achieves a 50% reduction in seizures in a variable number of patients (Englot et al., 2011).

Poorly controlled epilepsy exposes the patient to serious risk including injuries related to the seizures themselves, sudden unexplained death in epilepsy patients (SUDEP) and an overall increased mortality compared to otherwise healthy people (Beghi and Cornaggia, 2002). The definition of SUDEP includes deaths that are sudden, unexpected and without a toxicologist or anatomic cause at autopsy (Nashef, 1997 and Nashef et al., 2012). Categories of SUDEP based on the level of evidence available have been described (Annegers and Coan, 1999). The incidence of SUDEP varies from approximately 3 to 9 per 1000 patient-years with the lower estimates more typical of the broad epilepsy population and the higher ones more typical of more selected, poorly controlled populations (Hesdorffer et al., 2011; Ryvlin et al., 2011; Tomson et al., 2008; Tomson et al., 2005). Improvement in seizure control, either through adequate compliance with anti-seizure medications (Faught et al., 2008) or after successful resective surgery (Sperling et al., 1999), correlates with a reduced mortality risk.

There is an overall increased risk of injuries in patients with epilepsy. These injuries are most often related to falls and include fractures, and concussions. There is an increased risk of head injuries in patients with epilepsy. These are typically related to falls that may be due to the seizure itself or the underlying neurologic deficits related to the cause or treatment for the seizures. Although these head injuries may result in concussion, in prospective studies of poorly controlled epilepsy patients it is uncommon for a seizure to result in a head injury with scalp laceration (1.7%), skull fracture (0.0035%) or intracranial hematoma (0.007%) (Russell-Jones and Shorvon, 1989). Epilepsy, especially if poorly controlled, is associated with an increased risk of a number of psychiatric conditions both before and after the onset of the epilepsy (Hesdorffer et al., 2012; Rai et al., 2012). These include an increased incidence of suicide and related conditions such as depression. There is also an increased risk of a number of somatic disorders although for the most part these are attributable to disorders related to the cause of the epilepsy, risk factors common to both disorders, secondary effects of epilepsy treatment and the poor economic status of many of these patients (Gaitatzis et al., 2004 and Gaitatzis et al., 2012).

6. Overview of Clinical Studies

Data were collected in a feasibility study and a randomized prospective double blind multi-center pivotal clinical trial. During these studies, the NeuroPace® RNS® System was implanted in 256 subjects (65 subjects from the feasibility study and 191 subjects in the pivotal study). Subjects have been followed for 903.4 patient implant years and 819.5 patient stimulation years.

6.1. Feasibility Study

A feasibility study was performed to assess safety and to assess the effectiveness results for non-futility of proceeding to a pivotal study. The study design differed from that in the subsequent pivotal trial. The first four subjects implanted with the RNS Neurostimulator and leads at each clinical site participated in an open label protocol (N=42), and subsequent subjects (N=23) participated in a randomized, double-blind, concurrent Sham-stimulation control protocol in which the Treatment group received stimulation and Sham group did not. For the Treatment group, stimulation was enabled during the first 28 days post-implant (at the discretion of the investigator) and throughout the 12 week Evaluation Period. At the end of the 12 week Evaluation Period, all subjects received stimulation.

The primary safety endpoint was the incidence of serious adverse events (SAE) compared to the historical rate for deep brain stimulation for movement disorders (19% for the acute one month period after implantation and 36% for the short-term chronic period of 3 months after implantation (Oh et al., 2002; Summary of Safety and Effectiveness, Activa Tremor Control System P960009; Beric et al., 2001; Behrens et al., 1997; Hariz, 2002; Joint et al., 2002; Koller et al., 2001)). Safety data from the feasibility study was pooled with safety data collected during the pivotal study.

The primary effectiveness endpoint was a responder rate. A responder was defined as a subject with a 50% or greater reduction in overall seizure frequency. A responder rate of greater than 13% was considered adequate to support non-futility determination. Effectiveness was based on subject diary data from the last 84 days of the evaluation period compared to the data from the three 28-day periods immediately prior to implantation.

6.1.1. Feasibility Study: Subject Population

Subjects were between the ages of 18 - 65 years with partial onset seizures who had failed two or more antiepileptic drugs and had a minimum of 4 simple partial seizures (motor or sensory), complex partial seizures, and/or secondarily generalized seizures in each of the previous three months. Subjects were required to be on a stable antiepileptic medication regimen and must have previously undergone diagnostic testing that localized one or two epileptogenic region(s). Previous intracranial monitoring was not required. Subjects with psychogenic or non-epileptic seizures, status epilepticus, active psychosis, severe depression, or suicidal ideation within the preceding year were excluded, as were subjects who had therapeutic epilepsy surgery within the preceding 12 months or a cranial neurosurgical procedure within the previous month. Subjects with a Vagus Nerve Stimulator (VNS) were allowed to participate if the generator was left “Off” for at least 3 months prior to enrollment and explanted before or at the time of implantation with the RNS® System. The disposition of the 70 subjects enrolled in the feasibility study is shown in Table 1. Subjects were randomized by gender, temporal versus extratemporal seizure onset zone, and investigational site. There were 42 subjects treated in the open label phase. Note that the first 4 subjects at each site all received stimulation. Of the 23 randomized subjects, 9 were randomized

to the Treatment group, which received stimulation, and 14 were randomized to the Sham group, which did not receive stimulation until after the 12 week Evaluation Period.

Table 1. Feasibility Study – Subject Accountability Summary and Analysis Populations

Subject Population – Participation Profile	N
Total Subjects Enrolled	70
Subjects Withdrawn (pre-implant)	5
Total Subjects Implanted	65
Subjects Completing Evaluation Period (>4 months post-implant)[1]	65
Subjects Withdrawn (>12 months post-implant)	5
Subject Died (> 12 months post-implant)	1
Subjects Completing Participation (24 months post-implant)	59
Analysis Populations	**N**
Subjects in Safety Population	65
Subjects in Effectiveness Population, Total (Treatment group / Sham group)	65 (51 / 14)
Subjects in Open Label Population (not randomized, nonblinded; received responsive stimulation in an open label fashion following implant)[2]	42
Subjects Randomized to Treatment	9
Subjects Randomized to Sham	14

[1] Month = 28 days

[2] Two open label subjects did not have responsive stimulation therapy enabled in the four 28-day periods post-implant because they had no seizures following implantation.

Baseline demographic and clinical characteristics of the feasibility study population are listed in Table 2. Subjects had failed to achieve adequate seizure control after a mean of 8 anti-seizure drugs and approximately one-third had failed to achieve adequate seizure control after epilepsy surgery. Most had prior monitoring using intracranial electrodes.

Table 2. Feasibility Study – Baseline Demographics and Clinical Characteristics

Subject Characteristic	# Subjects Characterized (N)	Mean ± SD (min-max) or % (n/N)
Age at enrollment into Feasibility study (years)	59*	31 ± 10 (18 - 56)
Gender (Females)	65	52% (34/65)
Duration of epilepsy at enrollment into Feasibility study (years)	59*	17 ± 10 (2 - 42)
Number of AEDs Used Over Lifetime	65	8 ± 3 (2 - 15)
Prior Therapeutic Surgery for Epilepsy	65	37% (24/65)
Prior Intracranial Monitoring	65	82% (53/65)

* Due to hospital confidentiality requirements some institutions did not provide the date of birth for subjects.

6.1.2. Feasibility Study: Effectiveness

As seen in Table 3, there was a wide range of monthly seizure frequencies during the baseline, and post-implantation in the three groups: the Open label population (first four patients at each site;

all received stimulation), the Treatment group (randomized to receive stimulation), and the Sham group (randomized to not receive stimulation until after the 12 week Evaluation Period) groups.

Table 3. Feasibility Study – Seizure Frequency per Month During Baseline and from Implant through the Effectiveness Evaluation Period

		Open Label			Treatment			Sham Control		
		N (Range)	Mean	Median[1]	N (Range)	Mean	Median[1]	N (Range)	Mean	Median[1]
Baseline Months	0-1	42 (0 - 2861)	125.0	9.9	9 (3 - 1328)	182.0	9.0	14 (6 - 139)	29.6	14.0
	1-2	42 (0 - 2315)	109.0	10.0	9 (4 - 1067)	151.2	13.0	14 (4 - 90)	25.5	16.8
	2-3	42 (0 - 1741)	91.1	11.0	9 (5 - 1171)	163.6	12.0	14 (4 - 122)	27.7	13.0
Post-Operative Month	0-1	42 (0 - 2193)	87.0	6.3	9 (1 - 1016)	148.3	8.3	14 (2 - 169)	27.0	14.0
Effectiveness Evaluation Period Months	1-2	42 (0 - 2181)	86.2	6.5	9 (4 - 556)	90.7	7.0	14 (0 - 146)	25.3	5.7
	2-3	42 (0 - 2000)	79.4	8.0	9 (4 - 621)	98.4	8.0	14 (0 - 157)	25.9	4.5
	3-4	41 (0 - 1484)	76.4	9.0	9 (3 - 859)	119.1	6.0	14 (0 - 153)	25.5	6.7

[1] The large difference between mean and median seizure rates in the Open Label and Therapy On groups was driven by 2 subjects in the Open Label Group and one subject in the Therapy On Group who had high seizure rates compared to the rest of the subjects. Hence, medians are a better representation of the seizure rates within the respective groups.

The effectiveness objective was to demonstrate non-futility of proceeding to a pivotal trial. This objective would be met if the observed responder rate exceeded 13% at 4 months. As seen in Table 4, the responder rate for total disabling seizures (simple partial motor, complex partial and generalized tonic-clonic seizures) was 24%. Two subjects did not receive stimulation in the open label period because they became seizure-free following implant. The responder rate in the Sham group was 36%.

Table 4. Effectiveness endpoints for the feasibility study.

	Open (n=42)	Active (n=9)	Open +Active (n= 51)	Treatment received (n=49)	Sham (n=14)
Responder Rate	27%	11%	24%	22%	36%

6.1.3. Feasibility Study: Safety

The safety data from the feasibility study were assessed by the FDA in recommending approval of the pivotal study. Safety data from the feasibility study were pooled with data from the pivotal trial and are presented in Section 6.2.8.

6.1.4. Feasibility Study Conclusions.

Based on the responder rate in the Treatment group and safety data the sponsor concluded that a larger pivotal study was justified.

6.2. Pivotal Study Investigational Plan

The RNS® System Pivotal Clinical Investigation was a multi-center, prospective, randomized, double-blinded, Sham-stimulation controlled pivotal study designed to assess safety and effectiveness of the RNS® System. Based on the feasibility study results, the sponsor (a) changed the inclusion criteria by reducing the number of partial onset seizures required for inclusion from 4 to 3 per month and (b) increasing the blinded phase to 20 weeks.

To qualify for implantation with the RNS® System, the subjects were required to remain on a stable antiepileptic drug (AED) regimen while having an average of three or more disabling seizures (motor partial motor seizures, complex partial seizures and/or secondarily generalized seizures) per 28 days over three consecutive 28-day periods during the Baseline Period, with no 28-day period with fewer than two seizures.

Following is a summary of the study's eligibility criteria, efficacy and safety objectives, the measures used to evaluate the objectives, the sample size, and the study phases.

6.2.1. Pivotal Study - Eligibility Criteria

6.2.1.1. Inclusion Criteria

To participate in the study, the subjects are required to meet all of the following criteria:

- Subject has disabling simple partial motor seizures, complex partial seizures, and/or secondarily generalized seizures. Disabling refers to seizures that are severe enough to cause injuries, or significantly impair functional ability in domains including employment, psychosocial education and mobility.
- Subject has seizures that are distinct, stereotypical events that can be reliably counted, in the opinion of the investigator, by the subject or caregiver.
- Subject failed treatment with a minimum of two anti-seizure medications (used in appropriate doses) with adequate monitoring of compliance and the effects of treatment, as determined by the physician investigator.
- Subject has remained on the same antiepileptic medication(s) over the three most recent consecutive 28-day periods (other than acute, intermittent use of benzodiazepines). Subjects on the ketogenic diet are permitted if the diet has been stable for the preceding 12 weeks (three 28-day periods).
- Subject reports having an average of three or more disabling motor simple partial seizures, complex partial seizures and/or secondarily generalized seizures per 28 days over the three most recent consecutive 28-day periods, with no 28-day period with fewer than two seizures.
- Subject is between the ages of 18 and 70 years.
- Subject has undergone diagnostic testing as part of his/her standard care that has identified no more than two epileptogenic regions.
- A female subject of childbearing potential is using a reliable method of contraception (hormonal, barrier method, surgical or abstention), or is at least two years post-menopause.
- Subject or legal guardian is able to provide appropriate consent to participate.

- Subject can be reasonably expected to maintain a seizure diary alone or with the assistance of a competent individual.
- Subject is able to complete regular office and telephone appointments per the protocol requirements (including behavioral surveys and neuropsychological testing).
- Subject is willing to be implanted with a RNS® System as a treatment for his/her seizures.
- Subject is able to tolerate a neurosurgical procedure.
- Subject is considered a good candidate to be implanted with a RNS® System.

Note: A subject was still eligible to participate if antiepileptic medication(s) were temporarily discontinued for the purposes of diagnostic or medical procedures during the preceding 12 weeks.

6.2.1.2. Exclusion criteria

Subjects were excluded from study participation if they met any of the following criteria:

- Subject has been diagnosed with psychogenic or non-epileptic seizures in the preceding year.
- Subject has been diagnosed with primarily generalized seizures.
- Subject has experienced unprovoked status epilepticus in the preceding year.
- In the opinion of the investigator, the subject has a clinically significant or unstable medical condition (including alcohol and/or drug abuse) or a progressive central nervous system disease.
- Subject is taking chronic anticoagulants.
- Subject has been diagnosed with active psychosis, major depression or suicidal ideation in the preceding year. Subjects with post-ictal psychiatric symptoms need not be excluded.
- Subject is pregnant or planning on becoming pregnant in the next two years.
- Subject is enrolled in a therapeutic investigational drug or device trial.
- Subject has an implanted Vagus Nerve Stimulator (VNS) and is unwilling to have the VNS explanted (excluding leads) prior to or at the time of the RNS® System implant. (Subjects with VNS devices must have had VNS therapy discontinued for at least three months prior to enrollment.)
- Subject has had therapeutic surgery to treat epilepsy in the preceding 6 months. Subjects who have had epilepsy surgery (such as cortical resection, subpial transection or corpus callosotomy) more than 6 months ago are eligible.
- Subject has had a cranial neurosurgical procedure (including endovascular procedures) other than an epilepsy surgery involving the skull or brain in the previous 1 month.
- Subject is implanted with an electronic medical device that delivers electrical energy to the head.
- Subject is an unsuitable candidate for neurosurgery in the opinion of the investigator.
- Subject requires repeat MRIs in which the head is exposed to the radio frequency field.
- Subject's epileptogenic region(s) is/are located caudal to the level of the thalamus.
- In the opinion of the investigator, implantation of the RNS® System Neurostimulator and Lead(s) would present unacceptable risk.

6.2.1.3. Implant Criteria

A subject must meet the following criteria in order to be implanted with the RNS® System:

- Subject had an average of three or more disabling partial seizures per 28 days over the three most recent consecutive 28-day periods in the Baseline Period, with no 28-day period with fewer than two seizures.
- Subject remained on the same antiepileptic medication(s) over the three most recent consecutive 28-day periods (other than acute, intermittent use of benzodiazepines).

It should be noted that there were no inclusion or exclusion criteria based on the extent, accuracy or concordance of the diagnostic studies performed in an attempt to localize the potential epileptogenic focus or foci.

6.2.2. Implantation Procedure

The RNS® System is implanted under general anesthesia. The surgical procedure requires a craniectomy within which a Ferrule was attached and the Neurostimulator was placed. Depth and/or subdural Cortical Strip leads were placed via the craniectomy, or through a separate craniectomy or burr hole, depending on the location and orientation of the leads.
Subjects could have up to 4 leads implanted; however, only two depth leads could be implanted. Since the RNS ® System can only be connected to two Leads, if more than two leads were implanted; the proximal portion of the leads was externalized to the dura and capped. If epileptiform activity detection or stimulation response was not adequate with the 2 Leads initially selected, the third and/or fourth Lead could be connected to the Neurostimulator in place of the first and second Lead, without penetrating the dura. The criteria used for the location of the leads were not specified in the protocol.

Detection was enabled following initial implantation. Detection settings could be modified at subsequent visits during the post-implantation and stimulus optimization periods based on a review of the stored detections. Stimulation was activated for those subjects randomized to active stimulation at the visit 4 weeks after implantation. Stimulation parameters could be modified at subsequent visits based in part on whether simulation was or was not perceived by the subjects and whether after-discharges were detected.

6.2.3. Pivotal Study Objectives

The primary safety and efficacy objectives are to demonstrate that the RNS® System is safe and is effective as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures that are refractory to two or more antiepileptic medications.

6.2.4. Pivotal Study - Primary Efficacy Endpoint

The primary efficacy analysis was designed to establish superiority of the Treatment (‘Therapy ON’) group to the Sham (‘Therapy OFF’) group in reducing the frequency of total disabling seizures (simple partial motor, complex partial and generalized tonic-clonic seizures) during the Blinded Evaluation Period of the investigation.

The prespecified primary efficacy endpoint variable is the treatment-by-time interaction term in the generalized estimating equation (GEE) model using a Poisson distribution, where "treatment" refers to the Treatment group and "sham stimulation" to the Sham group and "time" refers to the Baseline Period or Blinded Evaluation Period. The dependent variable was each subject's daily seizure frequency during the Baseline and Blinded Evaluation Periods. The efficacy analyses (primary and secondary) use seizure data from the 84 days of the Baseline Period immediately preceding the date of qualification for Neurostimulator implant compared to the 84 days of the Blinded Evaluation Period. Using this model structure, the time effect assesses whether there was an effect of implanting the device, while the treatment-by-time interaction assesses whether the response over time for active stimulation treated subjects was the same or different from sham treated subjects.

Note that some of these alternate modeling assumptions were discussed between FDA and the Sponsor before the pivotal study was initiated. At that time, the FDA and sponsor agreed on the Poisson regression model. FDA raised the concern that there may be too many zero daily seizure counts during the 84-day interval, and recommended that monthly seizure counts be used. The Sponsor chose the daily model, stating that they expected many seizure-free days in the Treatment group, they did not think there was a clinically meaningful way of grouping data (e.g. monthly), that grouping data would obscure the variability that is typical of most subjects' seizure patterns, and that the presence many zeros would present no analytic difficulty to the GEE Poisson regression model. The Sponsor questioned the use of the Poisson model for grouped interval summaries.

6.2.5. Pivotal Study - Primary Safety Endpoint

The primary safety endpoint is the Serious Adverse Event (SAE) rate. The SAE rate was calculated for two time frames (acute and short-term chronic). The SAE rate is defined as the proportion of subjects having a serious adverse event. The objective is to establish that the RNS® System SAE rate is no worse than historical implantation of intracranial electrodes for localization procedures and epilepsy resective surgery rate and the historical Deep Brain Stimulator (DBS) rate for movement disorders from the published literature.

Safety of the RNS® System was demonstrated by analysis of serious adverse events:

- For the surgical procedure and following 28 days, the RNS® System serious adverse event rate is not expected to exceed 15%, which is comparable to the combined risks associated with implantation of intracranial electrodes for localization procedures and epilepsy resective surgery (Tanriverdi et al., 2009; Wong et al., 2009; Fountas and Smith, 2007; Hamer et al., 2002; Behrens et al., 1997). To demonstrate this, the upper limit of the one-sided 95% confidence interval for the RNS® System SAE rate was not to exceed 20%.

- For the surgical procedure and the following 84 days, the serious adverse event rate is not expected to exceed 36%, which is the three to four months rate for the DBS system for treatment of movement disorders (Oh et al., 2002; Summary of Safety and Effectiveness, Activa Tremor Control System P960009; Beric et al., 2001; Behrens et al., 1997; Hariz, 2002; Joint et al., 2002; Koller et al., 2001). To demonstrate this, the upper limit of the one-

sided 95% confidence interval for the RNS® System SAE rate was not to exceed 42%.

6.2.6. Pivotal Study - Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Comparison of the Treatment group responder rate to the Sham group rate over the 84-day Blinded Evaluation Period of the investigation. (Responder rate is defined as the proportion of subjects who experience a 50% or greater reduction in mean disabling seizure frequency compared to Baseline.)

- Change in average frequency of disabling seizures during the Blinded Evaluation Period versus Baseline for the Treatment group compared to the Sham group.

- Proportion of seizure-free days during the Blinded Evaluation Period versus Baseline for the Treatment group compared to the Sham-stimulation group.

- Change in seizure severity in individual subjects in the Blinded Evaluation Period versus Baseline as determined by the Liverpool Seizure Severity Scale (Baker et al., 1991). The Treatment group will be compared to the Sham group.

6.2.7. Pivotal Study- Secondary Safety Endpoints

The secondary safety endpoints were as follows:

- The rate of occurrence of any adverse event (AE) observed during each of the post-implant time periods: The Post-operative Stabilization Period, the Stimulation Optimization Period, the Blinded Evaluation Period and the Open Label Evaluation Period. Data are compared for Treatment versus Sham stimulation.

- Affective status (by summary scores from the Beck Depression Inventory (McNair et al., 1971), the Profile of Mood State (Beck et al., 1961) and the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) inventories) will be described for each treatment group for the Baseline and for the 84-day Blinded Evaluation Period of the investigation, as well as at three time points during the subsequent Open Label Evaluation Period (56-week, 80-week, and 104-week visits).

- Neuropsychological functioning as assessed by neuropsychological testing with validated, standardized inventories obtained pre-implant (within 28 days of the implant) and then at 20 weeks, 56 weeks and 104 weeks after implantation. The neuropsychological testing assessed visual and verbal memory, verbal fluency and naming, and cognitive flexibility.

- At the time of IDE approval, the sponsor prespecified in the clinical protocol that the SUDEP occurrence rate for the RNS® System would be no worse than 6.3/1000 patient years. This rate was based on the reported incidence of SUDEP which ranges from 3.5 deaths per 1000 person years in a population based cohort with epilepsy (Lhatoo et.al, 1991); 3.5/1000 patient years in a well-defined cohort of 4,700 patients (5,747 patient-years of exposure) included in the worldwide clinical development database of the antiepileptic drug lamotrigine (Leetsma

et.al., 1997); 4.5 per 1000 patient years for the Cyberonics Vagus Nerve Stimulator; 6 per l000 patient years in patients with medically refractory epilepsy followed in an epilepsy clinic (Sperling et.al., 1999); to 6.3 deaths per 1000 person-years in a population based Swedish cohort with refractory epilepsy who were candidates but did not choose to undergo epilepsy surgery (Nilsson et.al., 2003). The protocol stated that data from the RNS® System Feasibility Clinical Investigation, as well as the 5 year Long-term Treatment Investigation, would be used to collect approximately1500 patient years of data in order to confidently calculate the rate of Sudden Unexplained Death in Epilepsy (SUDEP).

The number of patient years necessary to determine that the 95% confidence interval for SUDEP does not exceed 6.3/1000 patient years can be calculated based on the number of patient deaths attributed to SUDEP that occur during the RNS® System Clinical Investigations and the number of patient years of data. As seen in Table 5 below, if there are 4 patient deaths identified as possibly or probably related to SUDEP, then 1446 years of patient follow-up will permit NeuroPace to be 95% confident that the true rate of SUDEP does not exceed 6.3/1000 patient years. After three SUDEP events, occurred the sponsor increased the acceptable SUDEP rate to 9.3per 1000 patient years.

Table 5. Follow-Up Required to Establish SUDEP Rate

K[1]	1	2	3	4	5	6
M[2]	823	1016	1231	1446	1657	1864

[1] K = number of deaths identified as possibly or probably related to SUDEP.
[2] M = number of patient years necessary to establish that the 95% confidence interval is < 6.3/1000 patient years.

6.2.8. Long-Term Efficacy and Safety Endpoints

Subjects are continued to be followed to gather long-term experience. The following endpoints were assessed:

- Change in average frequency of disabling seizures in the group originally randomized to the Sham-stimulation group (Therapy OFF) once therapy has been enabled in that group (Open Label Evaluation Period). Average seizure frequency during 84 days of the Open Label Evaluation Period will be compared to the average seizure frequency during the 84-day Blinded Evaluation Period.
- Each subject's responder status over the Open Label Evaluation Period.
- Daily seizure frequency counts compared to baseline during the Open Label Evaluation Period for both treatment groups.
- Quality of life in individual subjects as measured with the QOLIE-89 assessment inventory to provide a descriptive analysis for each treatment group for the Baseline, Blinded Evaluation, and Open Label Evaluation Periods.

6.2.9. Subset Analyses

Four subset analyses were pre-specified in the investigational plan: seizure onset location, number of seizure foci, previous resection, and antiepileptic medication changes.

- Seizure Onset Location: Subjects were stratified into two subsets, those with partial onset seizures of mesial temporal origin only versus partial onset seizures arising from any other region(s) of the cortex.
- Number of Seizure Foci: Subjects were stratified into two subsets, those with unifocal epileptogenic onsets and those with bi-focal onsets.
- Previous Resection: Subjects were stratified into two subsets, those with previous therapeutic surgery for epilepsy (including resection, subpial transection and/or corpus callosotomy) and those with no such surgery.
- Benzodiazepine Use: Subjects were stratified into two subgroups, those who used acute benzodiazepines as rescue medication for seizures during the Pre-Implant Period and those who did not.

6.2.10. Study Design

6.2.10.1. Phases

The study design is shown below in Figure 3. The study consisted of a Baseline Period (3 month minimum). Subjects who met the eligibility criteria were implanted with the RNS® System Neurostimulator and Leads. Following a 4-week post-operative recovery period, subjects were randomized 1:1 to receive active (Treatment group) or Sham stimulation (Sham group) in a blinded manner for 16 weeks during the blinded periods (Stimulation Optimization Period and Blinded Evaluation Period). Subjects in the Treatment group had their stimulation optimized over a 4 week period followed by 12 weeks of active stimulation. Detection and stimulation settings could be modified based on subject status, subject perception of stimulation (for the Treatment group) and the presence of after discharges (see Section 2 Device Description for a description of programming options). Subjects and the investigators collecting seizure data and other outcome data were blind to therapy allocation. Another group of investigators programmed the Neurostimulator but did not collect any of the outcome data. Following the blinded phase, subjects received open label stimulation during which all subjects received active stimulation and could have their antiepileptic medications changed.

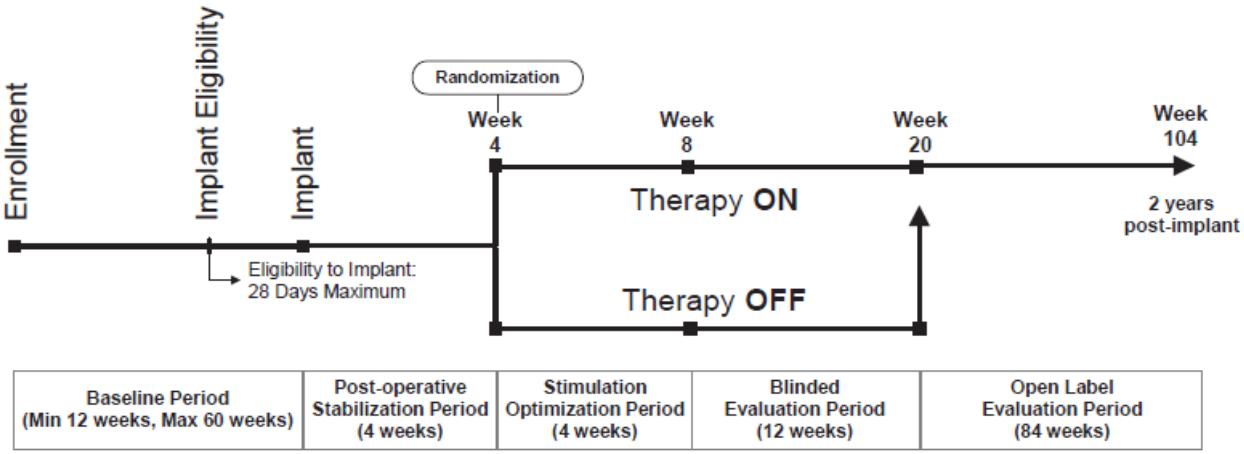


Figure 3. Timeline for RNS® System Pivotal Clinical Investigation

6.2.10.2. Schedule of Assessments

Subjects were evaluated at regular intervals throughout the trial. A detailed schedule of assessments is included in Table 61 in Section 12, Appendix I.

6.2.10.3. Sample Size

The sample size was calculated based upon the projected responder rate, where response is defined as a 50% reduction in the number of seizures per month from baseline to the end of the Blinded Evaluation Period. The trial was designed to have 80% power with an over-all 2-sided Type 1 error of 0.05, assuming responder rates in the Treatment group and Sham groups of 40% and 20%, respectively. To meet these criteria, 180 subjects were required in the Blinded Evaluation Period. Assuming approximately 10% of subjects would not be compliant (including subjects who did not complete the Blinded Evaluation Period), approximately 200 subjects were to be randomized, 100 each into the Treatment and Sham groups. Subjects who make changes the current number, type, and dosage of anti-epileptic drugs, subjects who do not come in for required follow-up visits, and females of child-bearing age who become pregnant all constitute non-compliance. Assuming a 20% dropout rate in the Baseline Period, a minimum of 240 subjects were planned to be enrolled in the investigation.

7. Pivotal Study Results

7.1. Subject Accountability

A total of 240 subjects were enrolled at 32 clinical sites. Table 6 summarizes the disposition of all enrolled subjects. Of the 240 subjects enrolled, forty-nine subjects withdrew prior to implant as detailed in the table.

A total of 191 subjects were implanted with the RNS® System Neurostimulator and Leads. All implanted subjects were randomized, 97 to active treatment and 94 to Sham stimulation. Both the Intent to Treat population and the Safety population consisted of these 191 subjects. Two subjects randomized to the Treatment group and two subjects randomized to Sham group exited during the Blinded Evaluation Period. One subject in each group withdrew after randomization (week 4) and before the Blinded Evaluation Period began, and one subject in each group withdrew after entering the Blinded Evaluation Period (weeks 8-20) (contributing one month or less of data during the Blinded Evaluation Period). One additional subject (Sham) withdrew during the Open Label Period of the study but had discontinued recording seizures after three months post-implant; this subject contributed one month of seizure data during the Blinded Evaluation Period.

As of June 4, 2010, 187 subjects completed the Blinded Evaluation Period (20 weeks post-implant), of whom 182 subjects have completed 12-months post-implant. 98 subjects have completed the Pivotal study (2 years post-implant), and 78 subjects continue to be followed in the Open Label Evaluation Period. Additional data in response to the major deficiency letter (see Section 4 above) was submitted on May 12, 2011. The safety data requested by the Center of Devices and Radiologic Health (CDRH) was limited to specific adverse events related to death, intracranial hemorrhage, psychiatric events, changes in seizures, and discontinuations.

Table 6. Pivotal Study – Enrollment and Subject Accountability Summary

Disposition	All Subjects	Treatment	Sham
Total Enrolled	**240**	N/A	N/A
Did not meet/maintain study I/E[1]	3		
Did not meet implant eligibility during Baseline Period[2]	4		
Withdrawn - Subject compliance failure	6		
Withdrawn - Physician preference	15		
Withdrawn - Subject preference	20		
Other[3]	1		
Implanted (ITT Safety Population), Week 0	**191**	N/A	N/A
Randomized (ITT Effectiveness Population), Week 4	**191**	**97**	**94**
Death	1	0	1
Withdrawn	1	1	0
Blinded Evaluation Period, Weeks 8 – 20			
Entered	**189**	**96**	**93**
Emergent explant	2	1	1
Completed	**187**	**95**	**92**
Open Label Evaluation Period, Weeks 20 – 52 (All subjects receive responsive stimulation)			
Entered	**187**	**95**	**92**
Death	3	2	1
Emergent explant	2	1	1
Completed	**182**	**92**	**90**
Open Label Evaluation Period, Weeks 52 – Completion (All subjects receive responsive stimulation)			
Entered	**182**	**92**	**90**
Death	2	1	1
Withdrawn	4	1	3
Not yet completed	**78**	**43**	**35**
Completed	**98**	**47**	**51**

[1] One subject did not meet seizure frequency requirements, one subject had more than two epileptogenic regions, and one subject had a clinically significant medical condition (alcohol abuse).

[2] Four subjects did not meet seizure frequency criteria (an average of 3 or more seizures per 28-day period over the past three consecutive 28-day periods, with no period with fewer than 2 seizures) during the Baseline Period.

[3] Site closed due to low enrollment.

Data as of June 4, 2010

7.2. Demographics and Baseline Characteristics

The average subject had epilepsy for more than 20 years, was taking more than two different AEDs per day and had a median frequency of more than 9 disabling seizures every 28 days. Demographic and baseline characteristics are provided in Table 7. There were no statistically significant differences between the Treatment and Sham groups with respect to these characteristics.

Table 7. Pivotal Study – Demographic and Baseline Characteristics (Implanted Subjects)

Characteristics	All Implanted (N = 191)		By Randomization Group				
			Treatment (N = 97)		Sham (N = 94)		P-value[1]
Female	48% (91/191)		48% (47/97)		47% (44/94)		0.820
	N	**Mean ± SD (Range)**	**N**	**Mean ± SD (Range)**	**N**	**Mean ± SD (Range)**	**P-value[2]**
Age (years)	191	34.9 ± 11.6 (18 - 66)	97	34.0 ± 11.5 (18 - 60)	94	35.9 ± 11.6 (18 - 66)	0.239
Duration of epilepsy (years)	191	20.5 ± 11.6 (2 - 57)	97	20.0 ± 11.2 (2 - 57)	94	21.0 ± 12.2 (2 - 54)	0.546
Number of antiepileptic drugs (AEDs) taken (at enrollment)	191	2.8 ± 1.2 (0 - 8)	97	2.8 ± 1.3 (1 - 8)	94	2.8 ± 1.1 (0 - 6)	0.976
Mean seizure frequency during Pre-Implant Period (seizures/day)	191	1.2 ± 2.2 (0.1 - 12.1) median = 0.35	97	1.2 ± 2.0 (0.1 - 10.5) median = 0.31	94	1.2 ± 2.4 (0.1 - 12.1) median = 0.42	0.875

[1] p-value per chi-square test
[2] p-value per two-sample t-test
Data as of June 4, 2010

7.3. Subset Populations of Interest

More than one third of the subjects had been treated with VNS, and one third had undergone previous resective epilepsy surgery (Table 8). Fifteen subjects in the Treatment group and 15 in the Sham group had had both VNS and prior epilepsy surgery. Intracranial electrodes had not been used for localization in 41% of the study population. Intracranial electrodes had been used in 65% of the Treatment group and in 53% of the Sham group (p = 0.098). A single seizure focus was found in 49% of the Treatment group and in 62% of the Sham group (p=0.089). The remaining baseline clinical characteristics, including prior therapeutic surgery, were well balanced between the two treatment groups. As seen in Table 9 below, baseline seizure frequency was influenced by seizure onset zone, the number of foci and prior therapeutic surgery.

Table 8. Pivotal Study – Subset Populations of Interest (Implanted Subjects)

Characteristics	All Implanted (N = 191)	By Randomization Group		
		Treatment (N = 97)	Sham (N = 94)	P-value[1]
Seizure onset location - Mesial Temporal Lobe Only (v. other)[2]	50% (95/191)	49% (48/97)	50% (47/94)	0.943
Number of seizure foci - Bifocal (v. unifocal)[2]	55% (106/191)	49% (48/97)	62% (58/94)	0.089
Prior therapeutic surgery for epilepsy[2]	32% (62/191)	35% (34/97)	30% (28/94)	0.437
Prior EEG monitoring with intracranial electrodes	59% (113/191)	65% (63/97)	53% (50/94)	0.098
Prior VNS	34% (64/191)	31% (30/97)	36% (34/94)	0.443
Anatomical brain abnormality (by neuroimaging)	67% (128/191)	68% (66/97)	66% (62/94)	0.759
Benzodiazepine use (acute)3	36% (69/191)	31% (30/97)	41%(39/94)	0.129

[1] p-value per chi-square
[2] Characteristics used as strata in adaptive randomization algorithm
[3] Subjects who used acute benzodiazepines as rescue medications for seizures at any time during the Pre-Implant Period up until the implantation procedure. Does not include daily use of benzodiazepines.

Table 9. Pivotal Study – Pre-Implant Period Mean Seizure Frequency by Subset Populations (Implanted Subjects)

	% (n/N)	Pre-Implant Seizure Frequency (Mean ± SD, seizures/month)
Seizure Onset Zone		
Mesial Temporal Lobe	50% (95/191)	15.81 ± 26.75
Other	50% (96/191)	52.39 ± 79.27
Number of Seizure Foci		
Unifocal onset	45% (85/191)	53.79 ± 84.65
Bifocal onset	55% (106/191)	18.49 ± 25.33
Prior Therapeutic Surgery for Epilepsy		
Prior Surgery	32% (62/191)	56.38 ± 85.30
No Prior Surgery	68% (129/191)	23.53 ± 43.21

7.3.1. Seizure Onset Location

One half of the subjects in the trial had seizures arising from the mesial temporal lobe. Of the remaining 50% of the subjects, 84% had onsets at non-mesial temporal neocortical locations only, and 16% had onsets in the neocortex as well as in a mesial temporal lobe. These characteristics were well balanced between the two treatment populations (Table 10).

Table 10. Pivotal Study – Seizure Onset Location (Implanted Subjects)

Onset Location	All Implanted (N = 191)	By Randomization Group	
		Treatment (N = 97)	Sham (N = 94)
	% (n/N)	% (n/N)	% (n/N)
Mesial Temporal Lobe Only	**50% (95/191)**	**49% (48/97)**	**50% (47/94)**
Other:	**50% (96/191)**	**51% (49/97)**	**50% (47/94)**
Neocortical Only	84% (81/96)	86% (42/49)	83% (39/47)
Neocortical + Mesial Temporal	16% (15/96)	14% (7/49)	17% (8/47)

Of the subjects with seizure onset in the mesial temporal region 73% had seizures arising from both the left and the right mesial temporal lobes (Table 11). Of those with unilateral mesial temporal onset, 18% of subjects had seizures arising from the left hemisphere and nine percent from the right temporal lobe.

Table 11. Pivotal Study – Onset Exclusively in Mesial Temporal Lobe (Implanted Subjects with Mesial Temporal Lobe Onsets, N=95)

Onset Hemisphere		Subjects with Onset in the Mesial Temporal Lobe (N = 95)	By Randomization Group	
			Treatment (N = 48)	Sham (N = 47)
		% (n/N)	% (n/N)	% (n/N)
Bilateral		73% (69/95)	69% (33/48)	77% (36/47)
Left	(w/ no prior resection)	15% (14/95)	15% (7/48)	15% (7/47)
	(w/ prior resection)	3% (3/95)	2% (1/48)	4% (2/47)
Right	(w/ no prior resection)	4% (4/95)	4% (2/48)	4% (2/47)
	(w/ prior resection)	5% (5/95)	10% (5/48)	0% (0/47)

7.3.2. Prior Therapeutic Surgery for Epilepsy

Of the 32% (62/191) of subjects who had undergone therapeutic epilepsy surgery, 58 had undergone a cortical resection, 7 subjects had a subpial transection and 2 subjects had a corpus callosotomy (Table 12). The differences in type of previous therapeutic surgery did not differ significantly between the two treatment groups.

Table 12. Pivotal Study – Types of Prior Therapeutic Surgery for Epilepsy (Implanted Subjects with Prior Therapeutic Surgery, N=62)

Surgery	Subjects with Prior Surgery (N = 62)	By Randomization Group	
		Treatment (N = 34)	Sham (N = 28)
	% (n/N)[1]	% (n/N)[1]	% (n/N)[1]
Resection	94% (58/62)	97% (33/34)	89% (25/28)
Subpial transection	11% (7/62)	12% (4/34)	11% (3/28)
Corpus callosotomy	3% (2/62)	0% (0/34)	7% (2/28)

[1] Some subjects had more than one type of surgery

7.3.3. Baseline Neuroimaging

Only 33% of subjects had normal neuroimaging at baseline. The most common abnormalities were mesial temporal sclerosis in 32% and the presence of dysplasia or a malformation in 21% of subjects (Table 13).

Table 13: Pivotal Study – Summary of Anatomical Brain Abnormalities by Neuroimaging (Implanted Subjects)

Abnormality Type	% of subjects (n/N)[1]
None	33% (63/191)
Sclerosis	32% (62/191)
Dysplasia or malformation	21% (40/191)
Encephalomalacia	5% (10/191)
Vascular abnormality	2% (4/191)
Surgical	2% (4/191)
Tumor	2% (3/191)

Abnormality Type	% of subjects (n/N)[1]
Unknown	2% (4/191)
Other[2]	5% (10/191)

[1] Some subjects had more than one type of anatomical brain abnormality

[2] Other anatomical brain abnormalities included: atrophy (3) /signal abnormality / traumatic /focal herniation / diffuse white matter abnormality / infarct / periventricular leukomalacia /parietal-occipital infarct / small hippocampal volume / cystic lesion.

7.3.4. Medical Conditions Co-morbid with Epilepsy

A summary of the pre-existing psychiatric and neurological conditions of the implanted subjects in the study is presented in Table 14. 49.7% of the subjects had a history of depression, 15.2% had a history of anxiety disorder, 5.2% had a history of suicidality, 27.2% had a history of memory difficulties, and 2.1% of subjects had a history of status epilepticus.

Table 14. **Pivotal Study – Pre-existing Psychiatric and Neurological Conditions Co-morbid with Epilepsy (Implanted Subjects, N=191)**

Pre-existing Condition		% of subject (# subjects)[1]
Psychiatric	Depression	49.7% (95)
	Anxiety	15.2% (29)
	Suicidality[2]	5.2% (10)
	Panic attack	3.7% (7)
	Psychosis/hallucinations	2.6% (5)
	Psychosis-post-ictal	2.6% (5)
	Bipolar disorder	1.0% (2)
Neurological	Headache/Migraine	65.4% (125)
	Memory deficits/disorder	27.2% (52)
	Ataxia/balance disorder	16.8% (32)
	Tremor	16.2% (31)
	Nystagmus	12.0% (23)
	Insomnia/Sleep	5.2% (10)
	Status epilepticus	2.1% (4)

[1] Percentage calculated based on available data for all implanted subjects (N=191).

[2] Suicidality includes suicidal ideation, thoughts, or gestures and suicide attempts

Data as of June 4, 2010

7.3.5. Antiepileptic Medications Including Acute Intermittent (Rescue) Benzodiazepines

As seen in Table 15, subjects in both arms of the trial maintained a stable regimen of antiepileptic drugs in the Pre-Implant Period through the end of the Blinded Evaluation Period.

Table 15. Pivotal Study – Benzodiazepine Use and Changes in AEDs, Pre-Implant through Blinded Evaluation Periods (Treatment and Sham)

Medication Changes[1]	Treatment (N=97) % (n/N) subjects		Sham (N=94) % (n/N) subjects	
	Pre-Implant Period Until Implant	Implant through Blinded Evaluation	Pre-Implant Period Until Implant	Implant through Blinded Evaluation
Allowed Per Protocol:				
Acute Benzodiazepine Use	31% (30/97)	34% (33/97)	41% (39/94)	43% (40/94)
Protocol Deviations:				
AED New	0%	1% (1/97)	1% (1/94)	1% (1/94)
AED Significant Increase	0%	1% (1/97)	0%	0%
AED Significant Decrease	1% (1/97)	0%	1% (1/94)	0%
AED Discontinued	0%	0%	0%	0%

[1] Differences in benzodiazepine usage and in changes in AEDs between Treatment and Sham are not significant (all p-values > 0.05 by Fisher's exact test).

7.4. Implantation Data

As seen in Table 16, 191 subjects were implanted. A total of 518 Leads (294 Cortical Strip Leads and 224 Depth Leads) were implanted in the initial procedure. As seen in Table 17, 58% of the subjects received two leads, 14% received 3 leads and 29% received 4 leads, with approximately one third of the subjects receiving only cortical leads, one third receiving only depth leads and one third receiving a combination of cortical and depth leads.

Table 16. Pivotal Study – Duration of Surgery for Initial Implantation of Neurostimulator and Leads

Number of implantation surgeries	191
Total number of Neurostimulators	191
Total number of Cortical Strip Leads	294
Total number of Depth Leads	224
Surgery duration in hours (Average ± SD, Range)	3.59 ± 1.38 (1.17 - 9.82)

Table 17. Pivotal Study – Leads Implanted at Time of Initial Neurostimulator Implantation (Treatment and Sham)

	All Implanted (N = 191)	By Randomization Group	
		Treatment (N = 97)	Sham (N = 94)
Number of Leads:	**% (n/N) of subjects**		
1	0% (0/191)	0% (0/97)	0% (0/94)
2	58% (110/191)	57% (55/97)	59% (55/94)
3	14% (26/191)	14% (14/97)	13% (12/94)
4	29% (55/191)	29% (28/97)	29% (27/94)
Types of Leads:	**% (n/N) of subjects**		
Cortical Strip Leads Only	31% (59/191)	31% (30/97)	31% (29/94)
Depth Leads Only	39% (74/191)	37% (36/97)	40% (38/94)
Cortical Strip and Depth Leads	30% (58/191)	32% (31/97)	29% (27/94)

The initial recommended stimulation settings were a frequency of 200 Hz, a pulse duration of 160 μs, and a 100 ms burst duration (Table 18). Subsequent changes in detection and stimulation parameters were not specified by the protocol. Stimulation settings could be modified by the investigator based on subject status, subject perception of stimulation (for the Treatment group) and the presence of after discharges. With the exception of 1 Hz frequency and 1000 μs pulse duration, subjects used the full range of available stimulation parameters.

Table 18. **Pivotal Study – Range of RNS® System Neurostimulator Programmable Stimulation Parameters Used in the Study**

	Minimum	Maximum
Current	0.5 mA	12 mA
Burst Duration	10 ms	5000 ms
Frequency	2 Hz	333 Hz
Pulse Width	40 μs	520 μs

7.5. Protocol Deviations

Ten subjects who withdrew from the Pivotal study before implantation did not meet the study inclusion/exclusion criteria at enrollment:

- Three subjects had antiepileptic medication changes over the three months prior to enrollment.
- Four subjects were not able to complete the behavioral surveys.
- Two subjects did not have a sufficient number of seizures before enrollment.
- One subject who was withdrawn because of alcoholism.

Eleven subjects who were implanted had not met the study inclusion/exclusion criteria at enrollment:

- Six subjects' antiepileptic medications were changed during the three months before enrollment.
- One subject was not able to complete the behavioral surveys.
- One subject did not have a sufficient number of seizures before enrollment.
- One subject had been diagnosed with suicidal ideation in the preceding year.
- One subject's VNS had not been turned off for a full 3 months prior to enrollment.
- One subject had not met two of the inclusion/exclusion criteria; antiepileptic medications had been changed over the three months prior to enrollment and the subject had been diagnosed with major depression in the preceding year.

Over the Pre-Implant Period, all 11 subjects met the criteria for implantation, including sufficient seizure frequency and stable antiepileptic medications during the 12-week Pre-Implant Period. Therefore, the sponsor believed the impact of these deviations on the primary endpoint evaluation was minimal and these subjects' data were included in the analyses.

There were nine subjects who had protocol compliance-related deviations which resulted in their data being excluded from the Per-Protocol Population:

- Two subjects did not meet implant eligibility criteria as they had fewer than 2 seizures during one of the three consecutive months of the Pre-Implant Period; each had a total seizure count of greater than 9 seizures during the three-month qualification period.
- One subject did not meet implant eligibility because a change was made to antiepileptic medications two months prior to implant, however this change was not reported to the clinical site until the Open Label Week 32 appointment.
- One subject had brain tissue (a portion of the hippocampus) intentionally removed during the implant procedure.
- Five subjects had a significant change in antiepileptic medications after qualification for implant and prior to the Open Label Period.

Fifty-seven (57) of the subjects who were implanted had a compliance deviation related to maintenance of the seizure diary. Usually the seizure diary was missing or the severity scale was incomplete. However, often seizure data had already been provided via a telephone appointment or the subject used their own personal seizure diary. Therefore, only 2% of the observations for the primary effectiveness endpoint analysis were missing.

8. Pivotal Study Safety Results and Analyses

8.1. Primary Safety Endpoint

The protocol defined two periods of adverse event occurrence following implantation, an "acute" period from implantation to week 4 after implantation and a "short term chronic" period from implantation to week 12 after implantation. The acute safety objective, i.e. post implant to 28 days, was to demonstrate that the RNS® System SAE rate was no worse than the SAE rate associated with implantation of intracranial electrodes and epilepsy surgery. The short term chronic safety objective, i.e. postimplant to week 12 was to demonstrate that the RNS® System SAE rate was no worse than the SAE rate associated with deep brain stimulation for movement disorders. For the "acute" phase the primary endpoint was an upper limit of the 95% confidence interval of 20% or less, and for the short-term chronic phase of 42% or less. Both endpoints were met as seen in Table 19. The SAE rates for these two periods are similar to those for the pooled study population of 256 subjects (see adverse event tables provided on CD).

Table 19. Pivotal Safety – Primary Safety Endpoint: Acute and Short- Term Chronic Serious Adverse Event Rates (Implanted Subjects)

Period	RNS® System SAE Rate	Comparator SAE Rate		Met primary safety endpoint?
	Observed Rate (% (n/N) subjects with ≥ 1 SAE) [upper CI][3]	**Intracranial electrodes/ epilepsy surgery**[1] [upper CI][3]	**DBS for movement disorders**[2] [upper CI][3]	
Acute (Surgery – Week 4)	12.0% (23 /191) [16.5%]	15% [20%]	--	Yes, upper limit for the RNS® System is less than that of the comparator: (16.5% < 20%)
Short-Term Chronic (Surgery – Week 12)	18.3% (35 /191) [23.4%]	--	36% [42%]	Yes, upper limit for the RNS® System is less

Period	RNS® System SAE Rate	Comparator SAE Rate		Met primary safety endpoint?
	Observed Rate (% (n/N) subjects with ≥ 1 SAE) [upper CI][3]	Intracranial electrodes/ epilepsy surgery[1] [upper CI][3]	DBS for movement disorders[2] [upper CI][3]	
				than that of the comparator: (23.4% < 42%)

[1] Protocol-specified endpoint, based on literature: SAE rate associated with implantation of intracranial electrodes and epilepsy surgery (Tanriverdi et al., 2009; Wong et al., 2009; Fountas and Smith, 2007; Hamer et al., 2002; Behrens et al., 1997).

[2] Protocol-specified endpoint, based on literature: SAE rate associated with deep brain stimulation for movement disorders (Oh et al., 2002; Summary of Safety and Effectiveness, Activa Tremor Control System P960009; Beric et al., 2001; Behrens et al., 1997; Hariz, 2002; Joint et al., 2002; Koller et al., 2001).

[3] Upper limit of the one-sided 95% confidence interval, estimated using the Score Interval (also known as the Wilson Interval (Zhou et al., 2008)). Upper limits for literature comparators were pre-specified in the protocol, estimated using the Score Interval based on a sample size of 180.

The Panel will be asked to comment on the overall safety profile of the device in the proposed population.

8.2. Overall Adverse Event Rate – Pivotal Trial

The overall incidence of adverse events, serious and non-serious ("mild") occurring from implantation to the end of the Blinded Evaluation period did not differ between the two treatment arms (Table 20). The sponsor has used the term "mild" for adverse events that were not considered serious. Serious adverse events were defined as events resulting in:

- "Significant risks or consequences to the subject's acute or long-term health, serious injury or death." or
- "Hospital admission or invasive intervention required to alleviate the adverse events."

"Mild" adverse events were defined as:

- Minor in nature or behavior.
- Acute and self-limited, or transient.
- No need for invasive medical or procedural intervention to alleviate the adverse event.
- Any adverse event that is not serious.

Table 20. Pivotal Safety – Summary of Percentage of Subjects with Adverse Events by Severity from Implant through Blinded Evaluation Period (Treatment vs. Sham)

	% (n/N) of subjects reporting ≥ 1 AE, Implant through Blinded Evaluation Period (20 Weeks)		
	Treatment (N=97)	Sham (N=94)	P-Value[1]
Serious AEs	**16.5% (16/97)**	**23.4% (22/94)**	**0.377**
Non-=Serious ("Mild") AEs	**92.8% (90/97)**	**89.4% (84/94)**	**0.917**
Total (Serious + Non-Serious) AEs	**92.8% (90/97)**	**93.6% (88/94)**	

[1] Comparison of percentage of subjects with AEs, Treatment vs. Sham, per Fisher's exact test.

Serious adverse events (SAEs) were most common during the early post-implantation period (Table 21). In the twenty weeks after implantation 55 serious adverse events occurred in 44 subjects, most commonly in the 4 weeks after implantation. SAEs occurred in 12% of subjects during the post-operative stabilization period. Following randomization SAEs occurred in 6.2% of the Treatment group and 6.4% of the sham group during the stimulation optimization period and in 4.2% of the Treatment group and 5.4% of the Sham group during the blinded evaluation period (Table 22). Non-serious ("mild") adverse events were common in all study periods. Most subjects experienced multiple non-serious adverse events during these periods. Although comparable to the incidence of SAEs with other invasive intracranial procedures such as placement of intracranial monitoring electrodes of placement of a device for deep brain stimulation, the majority of these SAEs would not be expected to occur in a comparable medically treated population with intractable epilepsy.

Table 21. Pivotal Safety – Summary of Adverse Events (Percentage of Subjects and Event Rates) by Severity and Device Relation, by Study Period (Implanted Subjects)

	Post-Op Stabilization Period (Weeks 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)
# of subjects entering interval / Implant years within interval	**191 / 14.7**	**191 / 14.6**	**189 / 43.0**
	% Subjects (# subjects)[1] Event Rate [# events][2]		
Serious AEs:			
Total	12.0% (23) 1.837 [27]	6.3% (12) 1.164 [17]	4.8% (9) 0.256 [11]
Non-Serious ("Mild") AEs:			
Total	71.7% (137) 23.333 [343]	46.6% (89) 11.575 [169]	68.3% (129) 6.163 [265]
Total (Serious + Non-Serious) AEs	76.4% (146) 25.170 [370]	51.3% (98) 12.740 [186]	69.8% (132) 6.419 [276]

[1] % Subjects = # subjects with event / number of subjects entering interval
[2] Event Rate = # events / implant years within interval
Data as of June 4, 2010.

Table 22. Serious Adverse Events (SAEs) During the Pivotal Trial by Study Phase

Study Phase	Study Time Period (weeks)	Treatment # subjects/N[1] (%)	Sham # subjects/N[1] (%)
Post-Operative Stabilization	0-4	23/191 12.0%	
Stimulation Optimization	4-8	6/97 (6.2%)	6/94 (6.4%)
Blinded Evaluation	8-20	4/96 (4.2%)	5/93 (5.4%)

[1] # of subjects entering the study phase (Note that the number of subjects finishing a phase was less than N in all phases but the Post-Operative Stabilization Phase)

8.3. Serious Adverse Events - Pivotal Trial

Serious adverse events (SAE) occurring during the pre-implant period (Table 23) are of interest in that they provide a comparator for the incidence of SAEs in subjects following implantation. SAEs occurred in 15 of 191 subjects during the baseline assessment of seizure frequency. Of note is the occurrence of one head injury related to a seizure and one SAE of multiple injuries due to a seizure.

Table 23. Pivotal Safety – Serious Adverse Events during Pre-Implant Period (Implanted Subjects, N=191)

Preferred Term	% Subjects with events (# subjects)	# Events [# ongoing]
Summary of All SAEs in this Period	**7.9% (15)**	**16 [1]**
EEG monitoring	1.6% (3)	3 [0]
Angiogram cerebral	0.5% (1)	1 [0]
Arthralgia	0.5% (1)	1 [0]
Cellulitis	0.5% (1)	1 [0]
Complex partial seizures	0.5% (1)	1 [1]
Complex partial seizures increased	0.5% (1)	1 [0]
Dural abscess	0.5% (1)	1 [0]
Head injury (dts)	0.5% (1)	1 [0]
Multiple injuries (dts)	0.5% (1)	1 [0]
Postictal state	0.5% (1)	1 [0]
Pyrexia	0.5% (1)	1 [0]
Septoplasty	0.5% (1)	1 [0]
Simple partial seizures increased (sensory)	0.5% (1)	1 [0]
Skin laceration	0.5% (1)	1 [0]

8.3.1. SAEs During the Acute Post-Implantation Period

The most common SAE during the “acute” or 4 week post-implantation stabilization period was implant site infection occurring in 5 subjects (2.6%) one of which resulted in explantation of the leads and stimulator. There were two additional SAEs due to effusion or discharge at the implantation site. There was one SAE of bacterial meningitis. Three subjects had an intracranial hemorrhage during this period, one extradural, one subdural and one intraparenchymal (Table 24). Although comparable to the incidence of SAEs with other invasive intracranial procedures such as placement of intracranial monitoring electrodes of placement of a device for deep brain stimulation, the majority of these SAEs would not be expected to occur in a comparable medically treated population with intractable epilepsy.

Table 24. Pivotal Safety – Serious Adverse Events during Post- Operative Stabilization Period (Implanted Subjects, N=191)

Preferred Term	% Subjects with events (# subjects)	# Events [# ongoing]
Summary of All SAEs in this Period	**12.0% (23)**	**27 [0]**
Implant site infection	2.6% (5)	5 [0]
Extradural haematoma	1.0% (2)	2 [0]
Hydrocephalus	1.0% (2)	2 [0]
Procedural headache	1.0% (2)	2 [0]

Preferred Term	% Subjects with events (# subjects)	# Events [# ongoing]
Apraxia	0.5% (1)	1 [0]
Biopsy brain	0.5% (1)	1 [0]
Cerebral haemorrhage	0.5% (1)	1 [0]
Complex partial seizures exacerbated	0.5% (1)	1 [0]
Depression suicidal	0.5% (1)	1 [0]
Device lead revision	0.5% (1)	1 [0]
Drug hypersensitivity	0.5% (1)	1 [0]
Dysphemia	0.5% (1)	1 [0]
Implant site discharge	0.5% (1)	1 [0]
Implant site effusion	0.5% (1)	1 [0]
Meningitis bacterial	0.5% (1)	1 [0]
Pneumothorax	0.5% (1)	1 [0]
Postictal state	0.5% (1)	1 [0]
Procedural vomiting	0.5% (1)	1 [0]
Subdural haematoma	0.5% (1)	1 [0]
Therapeutic agent toxicity	0.5% (1)	1 [0]

Data as of June 4, 2010.

8.3.2. SAEs from Randomization to the End of the Blinded Evaluation Period

Following the post-operative stabilization period subjects were randomized to Treatment or Sham stimulation. There was no difference in the incidence of SAEs between the two treatment groups during the stimulation optimization period (Table 25), during the blinded evaluation period (Table 26) or during the combined stimulation optimization and Blinded evaluation periods (Table 27). There does not appear therefore to be significant adverse effects from stimulation itself. There is one further SAE of implant site infection during this period. One subject in each group required lead removal and one in each group required device removal. There was one additional SAE of a subdural hematoma during this period.

Table 25. Pivotal Safety – Serious Adverse Events during the Stimulation Period (Treatment and Sham)

	Treatment (N=97)		Sham (N=91)	
Preferred Term	% Subjects with events (# subjects)	# Events [# ongoing]	% Subjects with events (# subjects)	# Events [# on-going]
Summary of All SAEs in this Period	**6.2% (6)**	**10 [2]**	**6.4% (6)**	**7 [1]**
Device lead revision	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Medical device removal (VNS)	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Arthralgia	--	--	1.1% (1)	1 [0]
Central venous catheterisation	1.0% (1)	2 [0]	--	--
Death	--	--	1.1% (1)	1 [0]
EEG monitoring	--	--	1.1% (1)	1 [1]

Preferred Term	Treatment (N=97)		Sham (N=91)	
	% Subjects with events (# subjects)	# Events [# ongoing]	% Subjects with events (# subjects)	# Events [# on-going]
Implant site infection (dts)	1.0% (1)	1 [1]	--	--
Meningioma benign	1.0% (1)	1 [0]	--	--
Non-cardiac chest pain	--	--	1.1% (1)	1 [0]
Psychotic disorder	--	--	1.1% (1)	1 [0]
Respiratory depression	1.0% (1)	1 [0]	--	--
Skin laceration (dts)	1.0% (1)	1 [0]	--	--
Subdural haematoma (dts)	1.0% (1)	1 [1]	--	--
Syncope	1.0% (1)	1 [0]	--	--

Data as of June 4, 2010.

Table 26. Pivotal Safety – Serious Adverse Events during the Blinded Evaluation Period (Treatment and Sham)

Preferred Term	Treatment (N=97)		Sham (N=91)	
	% Subjects with events (# subjects)	# Events [# ongoing]	% Subjects with events (# subjects)	# Events [# on-going]
Summary of All SAEs in this Period	**4.2% (4)**	**4 [0]**	**5.4% (5)**	**7 [1]**
Complex partial seizures increased	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Alcohol poisoning	1.0% (1)	1 [0]	--	--
Hernia pain	--	--	1.1% (1)	1 [0]
Implant site infection (dts)	--	--	1.1% (1)	1 [0]
Jaw fracture (dts)	--	--	1.1% (1)	1 [0]
Myocardial infarction	1.0% (1)	1 [0]	--	--
Nephrolithiasis	--	--	1.1% (1)	1 [0]
Pneumonia	1.0% (1)	1 [0]	--	--
Simple partial seizures (sensory)	--	--	1.1% (1)	1 [1]
Simple partial seizures increased (sensory)	--	--	1.1% (1)	1 [0]

Differences between the percentage of subjects in the Treatment group reporting the events and that in the Sham group were not significant (all p-values > 0.05 by Fisher's exact test).
Data as of June 4, 2010

Table 27. Pivotal Safety – Serious Adverse Events during the Stimulation Optimization and Blinded Evaluation Periods Combined (Treatment and Sham)

Preferred Term	Treatment (N=97)		Sham (N=94)	
	% Subjects with event (# subjects)	# Events [# ongoing]	% Subjects with events (# subjects)	# Events [# on-going]
Summary of All SAEs in this Period	**9.3% (9)**	**14 [2]**	**11.7% (11)**	**14 [2]**
Complex partial seizures increased	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Device lead revision	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Implant site infection (dts)	1.0% (1)	1 [1]	1.1% (1)	1 [0]
Medical device removal (VNS)	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Alcohol poisoning	1.0% (1)	1 [0]	--	--
Arthralgia	--	--	1.1% (1)	1 [1]
Central venous catheterisation	1.0% (1)	2 [0]	--	--
Death	--	--	1.1% (1)	1 [0]
EEG monitoring	--	--	1.1% (1)	1 [0]
Hernia pain	--	--	1.1% (1)	1 [0]
Jaw fracture (dts)	--	--	1.1% (1)	1 [0]
Meningioma benign	1.0% (1)	1 [0]	--	--
Myocardial infarction	1.0% (1)	1 [0]	--	--
Nephrolithiasis	--	--	1.1% (1)	1 [0]
Non-cardiac chest pain	--	-	1.1% (1)	1 [0]
Pneumonia	1.0% (1)	1 [0]	--	--
Psychotic disorder	--	--	1.1% (1)	1 [0]
Respiratory depression	1.0% (1)	1 [0]	--	--
Simple partial seizures (sensory)	--	--	1.1% (1)	1 [1]
Simple partial seizures increased (sensory)	--	--	1.1% (1)	1 [0]
Skin laceration (dts)	1.0% (1)	1 [0]	--	--
Subdural haematoma (dts)	1.0% (1)	1 [1]	--	--
Syncope	1.0% (1)	1 [0]	--	--

Differences between Treatment and Sham groups not significant (all p-values > 0.05 per Fisher's exact test).
Data as of June 4, 2010

8.4. Non-serious ("Mild") Adverse Events

8.4.1. Non-Serious ("Mild") AEs Prior to Implantation

The incidence of non-serious ("mild") adverse events during the pre-implant period provide a comparator for the events following implantation, "Mild" adverse events were relatively uncommon during the baseline period and for the most part the types of events were not unexpected for this population (Table 28). Of note, there were 7 subjects (3.7%) with a skin laceration and 6 subjects (3.1%) with 8 contusions during this period, underscoring the frequency of injuries in this population.

Table 28. Pivotal Safety – Adverse Events Occurring in ≥2.5% of Subjects during the Pre-Implant Period (Implanted Subjects, N=191)

Preferred Term	% Subjects with events (# subjects)	# Events [# ongoing]
Upper respiratory tract infection	4.2% (8)	8 [0]
Nasopharyngitis	3.7% (7)	7 [0]
Skin laceration (dts)	3.7% (7)	7 [0]
Contusion (dts)	3.1% (6)	8 [0]

8.4.2. Non-Serious ("Mild") AEs During the Acute Post-Implantation Period

Non-serious ("mild") adverse events in the post-implantation stabilization period (Table 29), and the stimulation optimization period (Table 30) were expected for these periods of time.

Table 29. Pivotal Safety – All Adverse Events in ≥2.5% of Subjects during the Post-Operative Stabilization Period (Implanted Subjects, N=191)

Preferred Term	% Subjects with events (# subjects)	# Events [# on- going]
Implant site pain	28.3% (54)	55 [4]
Procedural headache	23.6% (45)	45 [4]
Therapeutic agent toxicity	5.2% (10)	10 [1]
Headache	4.7% (9)	9 [1]
Procedural nausea	4.7% (9)	9 [0]
Implant site swelling	4.2% (8)	8 [0]
Postoperative constipation	3.7% (7)	7 [1]
Swelling face	3.7% (7)	7 [0]
Dizziness	3.1% (6)	6 [0]
Postoperative fever	3.1% (6)	6 [0]
Implant site infection[1]	2.6% (5)	5 [0]

[1] All implant site infections were serious adverse events
Data as of June 4, 2010

Table 30: Pivotal Safety – Adverse Events in ≥2.5% of Subjects during the Stimulation Optimization Period (Treatment and Sham)

	Treatment (N=97)		Sham (N=94)		
Preferred Term	% Subjects with events (# subjects)	# Events [# ongoing]	% Subjects with events (# subjects)	# Events [# ongoing]	P-value[1]
Headache	4.1% (4)	4 [1]	8.5% (8)	9 [1]	0.245
Nasopharyngitis	5.2% (5)	5 [0]	3.2% (3)	3 [0]	0.721
Depression	3.1% (3)	3 [0]	3.2% (3)	3 [3]	1.000
Implant site pain	2.1% (2)	2 [0]	3.2% (3)	3 [0]	0.679

[1] Comparison of percentage of subjects with events in Treatment vs. Sham groups per Fisher's exact test (as of June 4, 2010)

8.4.3. Non-Serious ("Mild") AEs from Randomization to the End of the Blinded Evaluation Period

During the 12 week Blinded Evaluation phase injuries attributed to seizures were seen more frequently in the Treatment group (Table 31). There were 7 subjects (7.3%) with 8 contusions in the Treatment group and 2 subjects (2.2%) with 2 contusions in the Sham group. There were 6 subjects (6.3%) with 6 skin lacerations in the Treatment group and 3 subjects (3.2%) with 3 skin lacerations in the Sham group. The incidence of an SAE of increased complex partial seizures occurred in 4.2% of the Treatment group and in 3.2% of the Sham group.

Table 31. Pivotal Safety – Adverse Events in _≥2.5% of Subjects during the Blinded Evaluation Period (Treatment and Sham)

	Treatment (N=97)		Sham (N=94)		
Preferred Term	**% Subjects with events** (# subjects)	**# Events** [# ongoing]	**% Subjects with events** (# subjects)	**# Events** [# ongoing]	**P- value[1]**
Nasopharyngitis	6.3% (6)	7 [0]	8.6% (8)	9 [0]	0.588
Headache	5.2% (5)	5 [2]	7.5% (7)	8 [3]	0.563
Contusion (dts)	7.3% (7)	8 [0]	2.2% (2)	2 [0]	0.170
Skin laceration (dts)	6.3% (6)	6 [0]	3.2% (3)	3 [0]	0.498
Complex partial seizures increased	4.2% (4)	4 [1]	3.2% (3)	3 [0]	1.000
Depression	5.2% (5)	5 [2]	2.2% (2)	2 [2]	0.445
Dysaesthesia	2.1% (2)	2 [0]	5.4% (5)	5 [1]	0.273
Influenza	4.2% (4)	4 [0]	3.2% (3)	3 [0]	1.000
Therapeutic agent toxicity	2.1% (2)	2 [1]	5.4% (5)	5 [0]	0.273
Vomiting	3.1% (3)	4 [0]	3.2% (3)	3 [0]	1.000
Upper respiratory tract infection	1.0% (1)	1 [0]	4.3% (4)	4 [0]	0.206

[1] P-value presents the statistical significance of the difference between the percentage of subjects in the Treatment group with events and that in the Sham group during the Blinded Evaluation Period per Fisher's exact test.
Data as of June 4, 2010.

8.5. Adverse Events of Special Interest During Pivotal Study to the End of the Blinded Evaluation

8.5.1. Death and SUDEP

Given the relatively low numbers of deaths including those considered due to SUDEP these events will be addressed using data pooled from all studies (see Section 8.6.1).

8.5.2. Intracranial hemorrhage

During the pivotal trial 5 serious adverse events of intracranial hemorrhages occurred (Tables 25 and 27). Four of the hemorrhages occurred during the post-implantation period and one during the Stimulation Optimization period. Although the incidence of intracranial hemorrhage is comparable to that seen with other implantation procedures these events are not typically seen in a comparable medically treated population and represent a clear risk of treatment with the device. The incidence of intracranial hemorrhage in the pooled population is discussed further in section 8.6.2.

8.5.3. Infections

A serious adverse event of implant site infection occurred in 7 subjects between implantation and the end of the Blinded Evaluation period. All resolved, including two subjects who required explant. The only other SAE of infection during this period was one subject with pneumonia. The incidence of infection in the pooled population is discussed further in section 8.6.3.

8.5.4. Psychiatric adverse events

During the period from implantation to the end of the Blinded evaluation period there was one serious adverse event of a "psychotic disorder". This event occurred in the Sham stimulation group. The incidence of psychiatric adverse events for the pooled population is discussed further in section 8.6.4.

8.5.5. Affective Status

Affective status was assessed with the Beck Depression Inventory (BDI-II), the Profile of Mood States (POMS), and the Center for Epidemiological Studies Depression Scale (CES-D). There were no differences between the Treatment and Sham groups on any of the three mood assessments, from baseline to the end of the blinded evaluation period, nor any difference between the Treatment and Sham stimulation groups. There is no indication that the implantation procedure or active stimulation resulted in any short term effect on affective status.

8.5.6. Neuropsychological Functioning

Cognitive testing revealed no differences between the Treatment and Sham group at the end of the blinded evaluation period compared to baseline, nor any difference between the Treatment and Sham stimulation groups (Table 62 in Section 12, Appendix I). There is no indication that the implantation procedure or active stimulation resulted in any short term alteration of cognitive function.

8.5.7. Adverse Events Related to Changes in Seizures.

There was no difference in the incidence of serious adverse events related to a change in seizures, i.e. new types of seizures, or an increase or worsening in severity of existing seizure types, when comparing the two treatment arms following randomization up to the end of the Blinded Evaluation Period. However there were relatively few such events in either group during this 4 month period. Nevertheless the lack of a clear difference suggests that stimulation was not causing a short term change in the seizures. This issue is reviewed for the pooled population in section 8.6.8.

8.6. Adverse Events of Special Interest During Overall and Long Term Study

To evaluate overall safety including long-term safety of the RNS® System data from the feasibility trial and the pivotal trial including the open label long term phase have been pooled.

8.6.1. Deaths and SUDEP

As of June 4, 2010, there were a total of nine subject deaths over all trials. 6 deaths were attributed to SUDEP, two to suicide and one due to lymphoma. There have been two additional

deaths as of October 24, 2012: one due to SUDEP and one due to status epilepticus. See Table 32 below for estimates of the SUDEP rate.

The Panel will be asked to comment on the observed SUDEP rate, to discuss it in the context of overall benefit-risk, and to provide labeling recommendations as needed.

Table 32. Deaths Attributed to SUDEP

SUDEP in candidates for epilepsy surgery (Dasheiff, 1991)	9.3 / 1000 patient years
SUDEP in RNS® System Trials (as of June 4, 2010)	8.5/1000 implant years (two-sided 95% C.I. 3.8 – 18.9 / 1000 implant years
SUDEP in RNS® System Trials (as of October 24, 2012)	6.6/1000 implant years (two-sided 95% C.I. 3.0 - 14.8 / 1000 implant years)

8.6.2. Intracranial Hemorrhage – Pooled Population

For the pooled study population there were 14 adverse events of intracranial hemorrhage in 13 subjects: 11 were serious (Table 33). Six subjects had hemorrhages in the post-operative period, 4 of which were serious. Of the four, two epidural hematomas and one subdural hematoma were surgically evacuated and one intraparenchymal hemorrhage was treated medically and was considered resolved within 7 days. Two additional intracranial hemorrhages were considered "mild". One was an epidural hemorrhage resulting in headache and aphasia that resolved within 7 days without surgical intervention. The other considered "mild" was an occipital intracranial hemorrhage at the site of a hippocampal depth lead that resulted in a "visual field cut" that resolved within 5 days. Four hemorrhages were attributed by the investigator to head trauma that occurred during a seizure (1 traumatic intracranial hemorrhage, and 3 subdural hematomas). Two of the four were surgically evacuated.

Table 33. Pooled Safety – All Intracranial Hemorrhage Adverse Events Post-Implant (N=256)

Adverse Event	**All Adverse Events (Serious and Non-Serious)**		**Serious Adverse Events**	
Preferred Term	**% Subjects with events** (# subjects)	**# Events** [# ongoing]	**% Subjects with SAEs** (# subjects)	**# SAEs** [# ongoing]
Summary of all intracranial hemorrhage and hematoma events	**5.1% (13)**	**13 [2]**	**4.3% (11)**	**11 [2]**
Cerebral haemorrhage	.0% (5)	5 [1]	1.6% (4)	4 [1]
Extradural haematoma	1.2% (3)	3 [0]	0.8% (2)	2 [0]
Subdural haematoma (dts)	1.2% (3)	3 [1]	1.2% (3)	3 [1]
Subdural haematoma	0.4% (1)	1 [0]	0.4% (1)	1 [0]
Traumatic intracranial haemorrhage (dts)	0.4% (1)	1 [0]	0.4% (1)	1 [0]

Data as of June 4, 2010.

The Panel will be asked to comment on the observed rate of intracranial hemorrhage, to discuss it in the context of overall benefit-risk, and to provide labeling recommendations as needed.

8.6.3. Infections

For the pooled study population 22 subjects had an adverse event of implant or incision site infection, 15 of which were serious. All were related to the implantation site (Table 34). Two of the subjects' events were related to seizure related trauma. 4 of these subjects had the neurostimulator and/or leads explanted.

Table 34. Pooled Safety – All Implant or Incision Site Infection Adverse Events Post-Implant (N=256)

Adverse Event	All Adverse Events (Serious and Mild)		Serious Adverse Events	
Preferred Term	**% Subjects with events** (# subjects)	**# Events** [# on- going]	**% Subjects with SAEs** (# subjects)	**# SAEs** [# on- going]
Summary of all implant or incision site infections	8.6% (22)	26 [4]	5.9% (15)	17 [4]
Implant site infection	5.5% (14)	16 [3]	4.7% (12)	14 [3]
Incision site infection	2.7% (7)	8 [0]	0.4% (1)	1 [0]
Implant site infection (dts)	0.8% (2)	2 [1]	0.8% (2)	2 [1]

Data as of June 4, 2010.

8.6.4. Psychiatric Adverse Events

For the pooled study population, psychiatric adverse events occurred in a total of 102 of 256 subjects (39.8%). Twenty-one of the 102 subjects had a total of 33 serious adverse events. Serious adverse events were related to depression (1 subject), suicidality (12 subjects), acute psychosis (2 subjects, 3 events in 1 subject), chronic psychosis (3 subjects), post-ictal psychosis (1 subject) and conversion disorder (2 subjects). The remaining psychiatric serious adverse events affected 1 subject each and were emotional distress, affect lability, agitation, alcohol abuse and alcohol withdrawal, and an episode of a visual hallucination.

There were 12 serious suicidality adverse events, including 2 persons who died by suicide (one subject committed suicide by multiple drug ingestion (subject not receiving stimulation) and the other by a gunshot wound to the head.) The other serious adverse events related to suicidality (some subjects had more than 1 adverse event) were: suicidal depression (6), suicide attempt (4), suicidal ideation (2) and suicidal behavior (1). Eleven of the 12 subjects with serious adverse events related to suicidality had a history of suicidality and/or depression or met depression criteria at baseline per BDI-II or CES-D. 56 subjects reported a depression AE. One subject had a serious AE of depression and 55 had mild AEs. The one serious adverse event was a brief hospitalization because of depression.

The Panel will be asked to comment on the observed rate of psychiatric adverse events and suicides/suicide attempts, to discuss them in the context of overall benefit-risk, and to provide labeling recommendations as needed.

8.6.5. Neuropsychological Functioning

Cognitive testing at the end of the blinded evaluation period for the Treatment and Sham groups and at 52 and 104 weeks after implantation compared to baseline for the Treatment and Sham groups combined did not show any indication of an adverse effect on a variety of cognitive domains as detailed in Tables 62 and 63 in Section 12, Appendix I.

8.6.6. Cognitive Adverse Events

There were 9 subjects in the Pivotal study that had mild adverse events related to confusion.

8.6.7. Memory Impairment

Sixteen (16) subjects had adverse events related to memory impairment, all of which were mild. Seven of these 16 subjects had a history of memory dysfunction and 11 of the 16 had memory deficits documented by neuropsychological testing obtained prior to implantation.

8.6.8. Adverse Events Related to Changes in Seizures

Events relating to new, increased, or exacerbated (more severe or longer duration) seizures were reported as adverse events. A seizure type was considered new if the subject had not experienced that type of seizure before. A specific type of seizure was considered increased if that seizure type was considered to be more frequent. A specific seizure type was classified as exacerbated if the severity or duration were increased. If a single report described both increased frequency and exacerbation of an existing seizure type, then that subject was considered to have two adverse events.

One hundred and forty-seven (147) subjects had 173 adverse events related to changes in seizures. Thirty-eight (38) subjects had 64 adverse events that were considered serious An increase in complex partial seizure frequency was seen in 6.3% of subjects, and an increase in generalized tonic-clonic seizures in 5.9% and of simple partial motor seizures in 1.6%. A serious exacerbation of complex partial seizures was seen in 1.2%, of generalized tonic-clonic seizures in 3.5% and of simple partial motor seizures in 0.4%. An SAE of a new seizure type occurred in 3 subjects (Table 35).

Table 35. Pooled Safety – Adverse Events Related to Change In Seizures Post-Implant (Implanted Subjects, N=256)

		All Adverse Events (Serious and Mild)		Serious Adverse Events	
Seizure Type[1]		**% Subjects with events (# subjects) [Patient IDs]**	**# Events [# ongoing]**	**% Subjects with SAEs (# subjects) [Patient IDs]**	**# SAEs [# ongoing]**
Summary of adverse events related to changes in seizures		**57.4% (147)**	**405 [173]**	**14.8% (38)**	**64 [9]**
Simple Partial Seizures (Sensory)	New[2]	11.7% (30)	36 [35]	0.4% (1)	1 [1]
	Increased[3]	5.5% (14)	19 [1]	0.8% (2)	2 [0]
	Exacerbated[4]	2.0% (5)	7 [0]	--	--
Simple Partial	New[2]	7.8% (20)	34[34]	--	--

Seizure Type[1]		All Adverse Events (Serious and Mild)		Serious Adverse Events	
		% Subjects with events (# subjects) [Patient IDs]	# Events [# ongoing]	% Subjects with SAEs (# subjects) [Patient IDs]	# SAEs [# ongoing]
Seizures (Motor)	Increased[3]	6.3% (16)	23 [4]	1.6% (4)	9 [0]
	Exacerbated[4]	3.9% (10)	13 [1]	0.4% (1)	1 [0]
Complex Partial Seizures	New[2]	12.9% (33)	47 [47]	0.4% (1)	1 [1]
	Increased[3]	22.3% (57)	87 [23]	6.3% (16)	18 [3]
	Exacerbated[4]	12.1% (31)	40 [9]	1.2% (3)	3 [0]
Generalized Tonic-clonic Seizures	New[2]	2.3% (6)	6 [6]	0.4% (1)	1 [1]
	Increased[3]	14.5% (37)	53 [8]	5.9% (15)	19 [2]
	Exacerbated[4]	13.3% (34)	40 [5]	3.5% (9)	9 [1]

[1] In this table, changes in atonic or tonic seizure types reported as adverse events were grouped with "Simple Partial Seizures (Motor)" if the original seizure type did not involve impairment of awareness or "Generalized Tonic-Clonic Seizures" if awareness was impaired.
[2] A new seizure of this type
[3] An increase in frequency of a seizure of this type
[4] An increase in severity or duration of a seizure of this type
Data as of June 4, 2010.

8.6.9. Status Epilepticus

There were 18 events of status epilepticus which occurred in 10 subjects (3.9%). Nine of the events were considered serious. Eleven of the 18 events were nonconvulsive status epilepticus. Nine subjects had one episode each (all serious) and one subject had 6 of these events. One subject experienced a non-serious episode of prolonged focal motor seizure (nonconvulsive status epilepticus) that occurred during test stimulation (threshold testing); the stimulation settings were changed and the episode resolved the next day.

8.6.10. Seizure-Related Injury

For the pooled population there were 343 events of injury related to a seizure occurring in 118 subjects (56.1%). Twenty-eight events occurring in 21 subjects (8.2%) were considered serious. Head injury due to a seizure occurred 25 times in 23 subjects (9.0%). Two of the events were considered serious. There were 4 serious intracranial hemorrhages, 3 subdural and one traumatic intracranial hemorrhage. Seventeen (17) subjects sustained skeletal bone fractures due to a seizure, 6 considered serious.

The Panel will be asked to comment on the instances of increased, worsening, or new seizures, to discuss them in the context of overall benefit-risk, and to provide labeling recommendations as needed.

8.7. Neurostimulator Replacement/Explant

The reasons for neurostimulator replacement or explant are shown in Table 36. One hundred and eighty-six (186) of the 214 replacements were due to expected battery depletion. The Kaplan-Meier

estimate of the median time to replacement due to expected battery depletion was 2.2 years. Eleven (11) neurostimulators were explanted or replaced due to infection or erosion. Ten (10) neurostimulators were replaced during a procedure for lead revision. Ten (10) neurostimulators were replaced due to premature battery depletion. Other reasons for Neurostimulator explant or replacement included discontinuations with explant (11), CSF leak (1), intracranial monitoring (1), and presumed malfunction (1). Another Neurostimulator was found to be non-functional immediately upon implantation (at a replacement procedure); the device was removed and replaced before the operative site was closed. No reasons were provided for 3 additional replacement procedures.

There were 21 explantation procedures: 8 cases due to infection (2 to be reimplanted at a later date), 2 due to scalp erosion at the incision site (both to be re-implanted at a later date), 1 because of a hemorrhage, 1 because of a seizure-related scalp laceration that exposed the Neurostimulator, 9 because of an elective withdrawal from the study

Table 36. NeuroStimulator Explant or Replacement Reasons

Reason	Surgical Procedure		
	Device Explant	Device Replacement	Total
Expected battery depletion	0	186	186
Infection or skin erosion	9	2	11
Lead revision	0	10	10
Premature battery depletion	0	10	10
Other[1]	12	6	18
Total	**21**	**214**	**235**

[1] Other includes discontinuation with explant (11), no reason provided (3), CSF leak (1), intracranial monitoring (1), not implanted (1), and presumed malfunction (1).

Data as of June 4, 2010.

8.8. Lead Revisions

Table 37 below provides a summary of reasons for lead revisions. The most common type of Lead "revision" was to change the Leads that were initially connected to ones that had been previously implanted but not connected at the initial surgery. There were 8 procedures to replace or revise a total of 10 damaged Leads in 7 subjects. One subject's leads passed between the skull and a titanium plate and required 2 procedures to replace damaged Leads; during the first procedure, 2 damaged Leads required replacement, during the second procedure, 1 damaged Lead required replacement. A second subject also required 2 Leads to be revised; during a routine Neurostimulator replacement procedure, the 2 Leads that were originally connected to the Neurostimulator were inadvertently cut and the Neurosurgeon connected the other 2 previously implanted and intact Leads to the Neurostimulator. The remaining 5 subjects each underwent one surgical procedure to replace one damaged Lead.

There were 7 procedures; in which the Leads were explanted or abandoned due to infection or skin erosion. There were 25 procedures in which the Leads were revised to change the location for sensing and stimulation. In 17 of the procedures a previously implanted lead was connected. In 8 cases, the Lead revision was performed to improve Lead placement over the epileptogenic region: in 5 procedures, new Leads were implanted (3 were Lead replacements and 2 were new Lead implants), and in 3 procedures, previously implanted Leads were repositioned. After 3 years, approximately 13% of Lead sets were revised for this reason. There were an additional 9 lead revision procedures. No

reason was given for 7 of the procedures which included 4 newly implanted leads and 3 changes in lead connection. The reasons for the other two were CSF leak and high impedance. There were 12 procedures in which leads were explanted or abandoned; 11 were due to subject discontinuation and 1 for intracranial monitoring.

Table 37. Lead Revision Reasons

Reason for Revision	Total Number of Lead Sets
Lead damage	8
Infection or skin erosion	7
Change in Lead placement or connection	25
Other – Lead implants and replacements [no reason given (7), CSF leak (1), high impedance (1)]	9
Other – Lead explants (or abandoned) [discontinuation with explant (11), intracranial monitoring (1)]	12

Data as of June 4, 2010

8.9. Other Neurosurgical Procedures

There were three other neurosurgical procedures during the Long-Term Treatment trial. One subject had a cranioplasty to repair a skull defect after removal of an RNS® System Neurostimulator, and two subjects underwent therapeutic resective epilepsy surgeries. One of these subjects had a right amygdalo-hippocampectomy 1267 days after initial implant. The Neurostimulator and a right temporal Depth Lead were left in place and the subject continued to be treated with responsive stimulation. The second subject had a resection of a seizure focus 1504 days after initial implant. The Neurostimulator and Leads were left in place and the subject continued to receive responsive stimulation.

8.10. Withdrawals/Discontinuations

As of June 4, 2010, a total of fifteen subjects had discontinued the study. As of May 12, 2011, 43 subjects discontinued treatment. 8 were explanted because of infection or hemorrhage, 3 subjects were lost to follow-up, 9 subjects died and 23 subjects withdrew electively. An additional two subjects have died since May 12, 2011, bringing the total to 45 subjects who had discontinued treatment. The reasons for elective withdrawal included: to pursue other treatments (13), because the reduction in seizures was not sufficient (4), and because the subject did not want to have the Neurostimulator replaced when the battery reached expected end of service (3). Another subject had a seizure-related fall that caused a scalp laceration that exposed the Neurostimulator: this subject chose not to have the laceration sutured and withdrew from the trial. Another subject was withdrawn because the physician felt that the subject was no longer a suitable candidate to participate because of psychiatric issues not related to treatment with the RNS® System. The reason for withdrawal for one subject was not specified.

9. Pivotal Study Efficacy Results and Analysis

All 191 subjects implanted during the Pivotal investigation were included in the intent-to-treat analysis. 97 subjects were in the Treatment Group and 94 subjects were in the Sham Group.

The Panel will be asked whether they believe that the data provide a reasonable assurance that the device is effective for use in patients who meet the criteria specified in the proposed indication.

9.1. Therapy Allocation – Randomization Methods

Subjects implanted with the RNS® System Neurostimulator and Leads were randomized 1:1 to Treatment or Sham stimulation. To ensure equal representation in the two therapy groups, an adaptive randomization approach (minimization) was used to balance variables that might influence the clinical response to responsive stimulation. These variables (listed in order of priority) were:

1) Investigational site;
2) Seizure onset zone location (partial onset seizures of mesial temporal origin versus partial onset seizures arising from any other region of the cortex);
3) Number of seizure foci (unifocal versus bifocal); and
4) Previous resection (whether the subject had previously undergone a therapeutic epilepsy surgery.)

9.2. Interim Analysis

A pre-specified interim analysis was included in the protocol. This analysis was to occur after 90 subjects had completed the Blinded Evaluation Period to determine whether the primary effectiveness endpoint had been met early. However, the sponsor decided not to perform the interim analysis.

9.3. Blinding Assessment

A blinding assessment was performed at the end of the Blinded Evaluation Period. Subjects were asked whether they thought they had been receiving stimulation therapy, were not receiving stimulation therapy, or whether they did not know. Subjects were also asked the reason for their choice. The results of the blinding assessment, presented in Table 38, suggest that the blind was adequate as there was no significant pattern of subject guessing. Twenty-four percent (45/187) of the subjects said that they did not know. Of the remaining 142 subjects, 44% (62/142) guessed incorrectly and 56% (80/142) guessed correctly. Only one instance of breaking of the blind occurred. In this case, an assessment clinician was accidentally informed of a subject's therapy randomization status at the Blinded Evaluation Week 12 Office Appointment. In this case, another blinded investigator performed the remaining assessments.

Table 38. Pivotal Study – Blinding Assessment

Therapy Allocation	Subjects' Guessed Response		
	Receiving stimulation	Not receiving stimulation	"Don't Know"
Randomized to Treatment group (total assessed 96)	42[1]	31[2]	23[3]
Randomized to Sham group (total assessed 91)	31[2]	38[1]	22[3]

[1] Correct guess – total 80 subjects (80/187 = 43%)
[2] Incorrect guess – total 62 subjects (62/187 = 33%)
[3] Declined to guess – total 45 subjects (45/187 = 24%)

9.4. Primary Effectiveness Analysis

9.4.1. Observed Data

9.4.1.1. Group Level Response

As seen in Table 39, a total of 97 and 94 patients entered the Pre-Implant Period in the Treatment and Sham Group, respectively. During that period, the median pre-implant seizure frequency in the Treatment group was 8.7 and the range was from 3 to 294.7. The median pre-implant seizure frequency in the Sham group was 11.6 and the range was from 3 to 338. During the blinded phase, the Treatment median seizure frequency was 5.8 with a range from 0 to 226.8 and the Sham was 7.6 with a range from 0.3 to 446.6. In addition, the seizure frequency range during month 4-5 in the Sham group was 0 to 799. Figure 4 below depicts the mean seizure frequency per month (pre-Implant through Blinded Evaluation Period) for the Treatment and Sham groups and Figure 5 depicts the percent change in seizure frequency per month for Treatment and Sham groups.

Table 39. Pivotal Effectiveness – Seizure Frequency per Month Pre-Implant and Blinded Evaluation Periods

		Treatment			Sham		
		N	Mean	Median (Min - Max)	N	Mean	Median (Min - Max)
Pre-Implant Months	0-1	97	34.5	9.3 (2.0 - 305.0)	94	28.7	10.0 (1.0 - 283.0)
	1-2	97	34.3	9.0 (2.0 - 294.0)	94	34.5	12.0 (2.0 - 342.0)
	2-3	97	31.7	9.0 (0.0 - 350.0)	94	41.5	11.5 (2.0 - 634.0)
Pre-Implant Period		97	33.5	8.7 (3.0 - 294.7)	94	34.9	11.6 (3.0 - 338.0)
Post-Implant Months	2-3	96	22.9	6.5 (0.0 - 226.0)	93	27.1	8.3 (0.0 - 369.4)
	3-4	95	22.8	6.0 (0.0 - 266.0)	90	28.9	8.3 (0.0 - 336.0)
	4-5	95	21.4	6.0 (0.0 - 226.0)	91	35.4	7.0 (0.0 - 799.0)
Blinded Evaluation Period		96	22.4	5.8 (0.0 - 226.8)	93	29.9	7.6 (0.3 - 446.6)

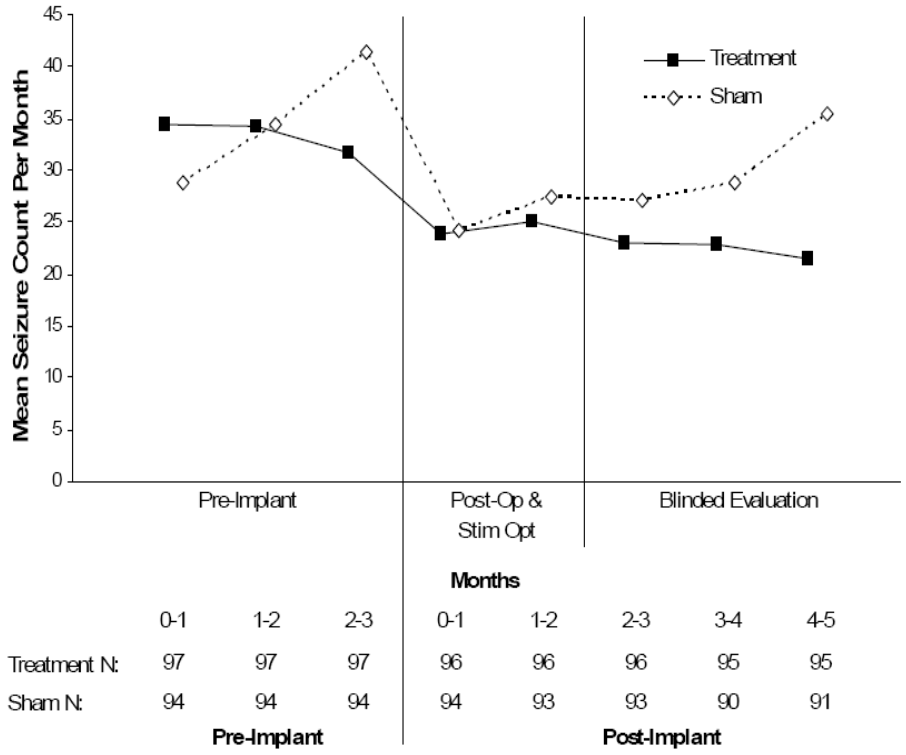


Figure 4. Mean Seizure Frequency per Month (Pre-Implant through Blinded Evaluation Period)

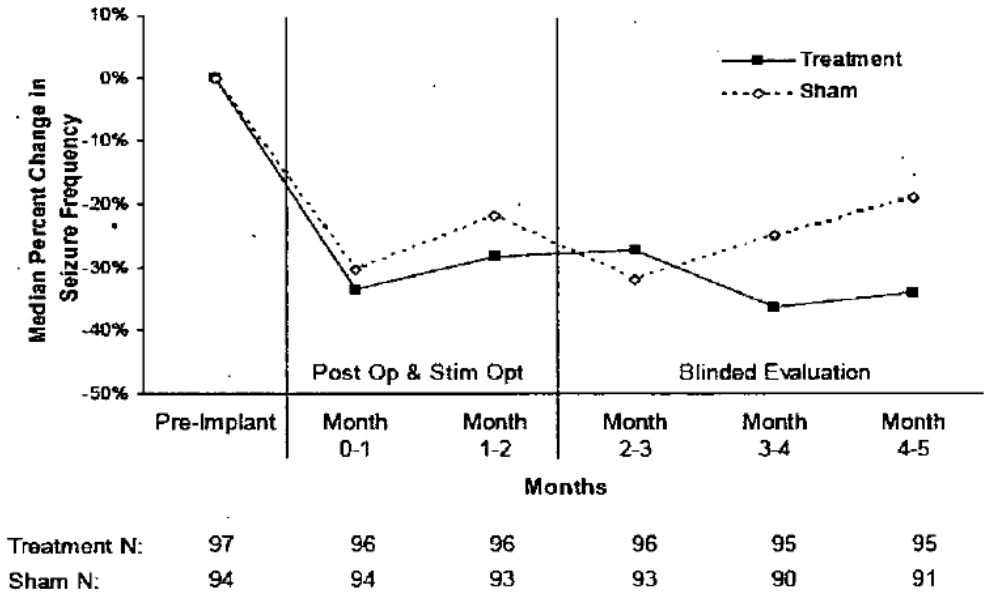


Figure 5. Median Percent Change in Seizure Frequency

9.4.1.2. Individual Subject Success

Figures 6 and 7 below contain a distribution of subject results. Seventy-six percent (76%) of subjects in the Treatment group and 70% in the Sham group reported a decrease in seizures during the Blinded Evaluation Period. There were 4 subjects in the Treatment group and 10 subjects in the Sham group who experienced a greater than 50% increase in seizures during the Blinded Evaluation Period. Figure 8 shows the combined results for the Treatment and Sham subjects.

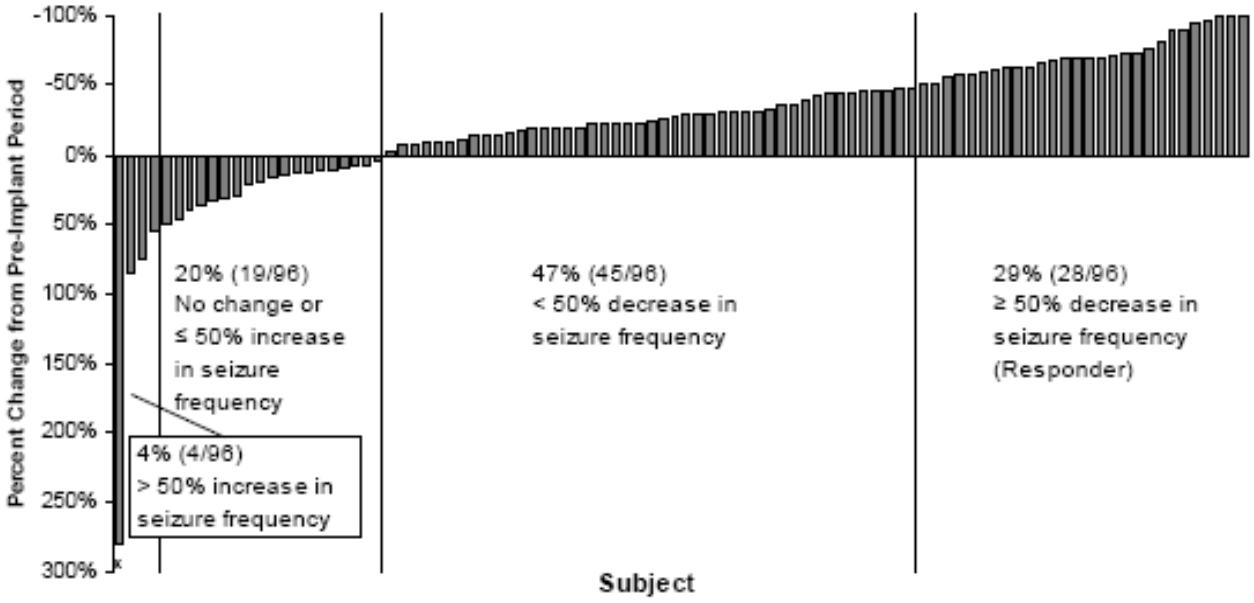


Figure 6. Pivotal Study – Seizure Frequency Percent Change by Subject Blinded Evaluation vs. Pre-Implant Treatment Group (N=96) (Negative values indicate a reduction in seizure frequency compared to Pre-Implant Period; X = subject withdrew from the trial during the Blinded Evaluation Period; the subject had only 1 diary day of data during the Blinded Evaluation Period, and 1 seizure was reported on that day, resulting in an artificially large estimate of seizure rate during the Blinded Evaluation Period.)

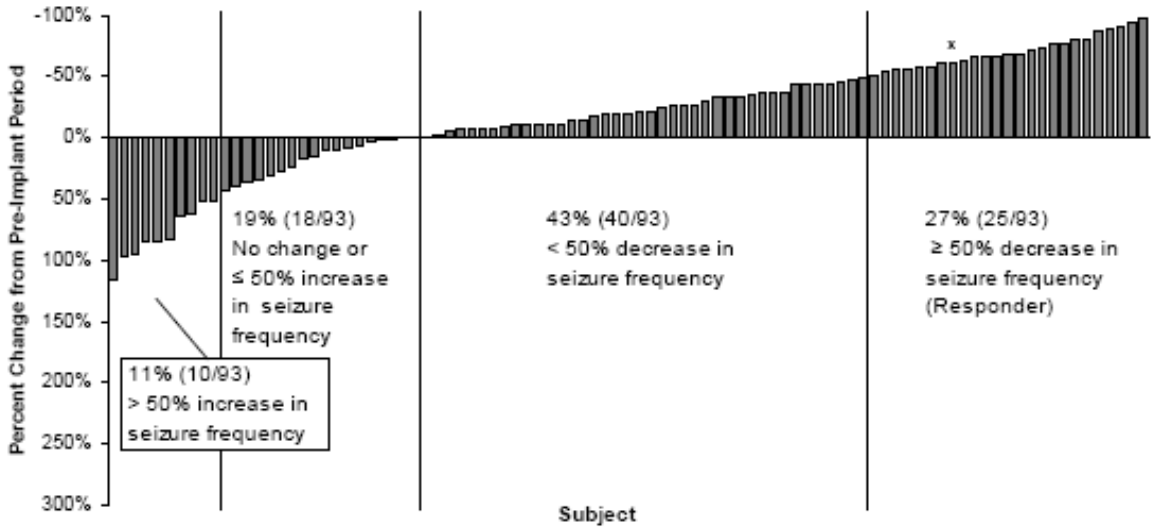


Figure 7. Pivotal Study – Seizure Frequency Percent Change by Subject Blinded Evaluation vs. Pre-Implant Sham Group (N=93) (Negative values indicate a reduction in seizure frequency compared to Pre-Implant Period; X = subject withdrew from the trial during the Blinded Evaluation Period)

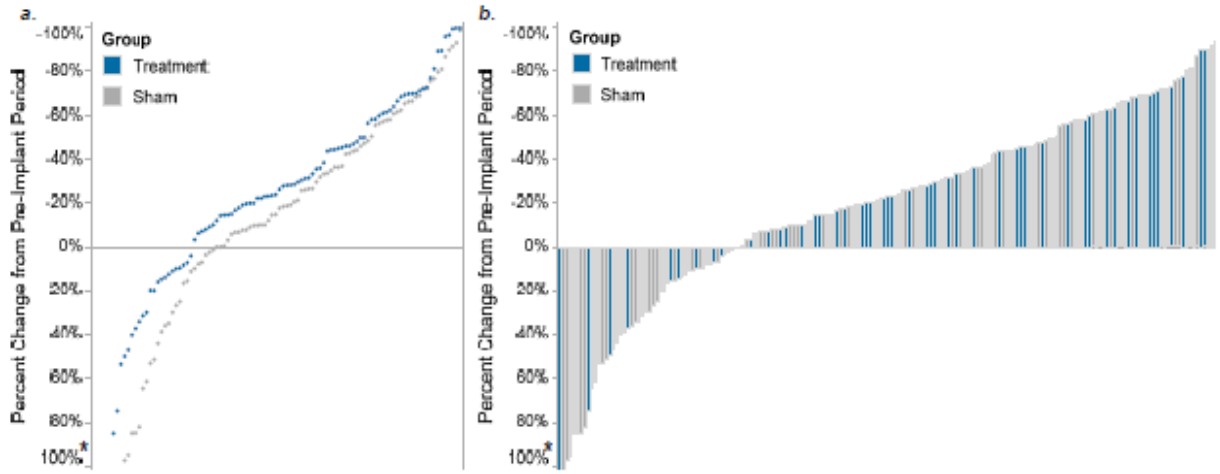


Figure 8. Combined Results for the Treatment and Sham Subjects

9.4.2. Pre-specified Primary Effectiveness Endpoint – Analysis

The pre-specified GEE analysis was to be based on daily seizure counts during the Pre-Implant and Blinded Evaluation Periods. There are two standard error estimation methods for the pre-specified analysis, empirical and model-based method[1]; however, neither the protocol nor the

[1] As discussed in the statistical Appendix, the model-based estimate assumes that the model is correctly specified, while the empirical estimate adjusts/calibrates the model-based estimate by the observed variability in the data.

statistical analysis plan (SAP) explicitly stated which method would be used. In this case, these two methods yielded distinctly different p-values (empirical p=0.15 vs. model-based p<0.0001).

Both the sponsor and CDRH agreed that such a discrepancy between the model-based and empirical p-values is typically indicative of a poor fit of the model to the data. As a result, both the sponsor and CDRH agreed that an alternative analysis model was needed.

Same treatment effect estimate, different p-values

The width of a confidence interval around an estimate is determined by the size of standard error estimate. Although using both empirical and model-based method the pre-specified model yielded the same treatment effect estimate, the standard error estimate differed. The model achieved statistical significance when using the model-based approach (p<0.0001), but not with the empirical standard error approach (p=0.15). Large difference between these p-values indicates a lack-of-fit of the pre-specified model.

9.4.3. Post Hoc Primary Effectiveness Endpoint Analysis

The pre-specified GEE model assumed that daily seizure count data would follow a Poisson distribution; however, the variability observed in the study exceeds the variability the Poisson distribution anticipates as a result of a large variability in day to day seizure counts in most subjects, as well as a large variability between subjects.

As seen in Table 40, seizure frequency in subjects with seizures arising in the mesial temporal lobe was lower than in subjects with seizures arising elsewhere. Subjects with unifocal onset had more frequent baseline seizures on average than did those with bifocal onset. The majority of subjects with bifocal onset had bilateral mesial temporal onset whereas the majority of unifocal subjects had seizures beginning in the neocortex. Seizure frequency was also higher in subjects with a prior epilepsy surgery than in those who had never had a surgery.

Table 40. Pivotal Study – Pre-Implant Period Mean Seizure Frequency by Subset Populations (Implanted Subjects)

	% (n/N)	Pre-Implant Seizure Frequency (Mean ± SD, seizures/month)
Seizure Onset Zone		
Mesial Temporal Lobe	50% (95/191)	15.81 ± 26.75
Other	50% (96/191)	52.39 ± 79.27
Number of Seizure Foci		
Unifocal onset	45% (85/191)	53.79 ± 84.65
Bifocal onset	55% (106/191)	18.49 ± 25.33
Prior Therapeutic Surgery for Epilepsy		
Prior Surgery	32% (62/191)	56.38 ± 85.30
No Prior Surgery	68% (129/191)	23.53 ± 43.21

As a result, the empirical estimate is more robust to model misspecification, at the cost of a reduction in efficiency.

The sponsor made the following post hoc modifications to the pre-specified GEE analysis (these issues are discussed further in the Statistical Appendix):

1. Using monthly rather than daily seizure count data
2. Modeling data with a negative binomial distribution rather than a Poisson distribution
3. Including the following clinical covariates used in the adaptive randomization:
    a. Seizure onset zone location (subjects with seizure onsets exclusively in the mesial temporal lobe versus any other region(s) of the cortex)
    b. Number of seizure foci (unifocal versus bifocal)
    c. Prior therapeutic epilepsy surgery (resection, subpial transection and/or corpus callosotomy, versus no such surgery)

Using the overdispersed Poisson model with monthly seizure counts rather than daily seizure counts, the post hoc GEE analysis did not achieve statistical significance (p=0.28). A comparison of Treatment versus Sham data using monthly seizure counts and the negative binomial rather than daily seizure counts and an overdispersed Poisson distribution also did not achieve statistical significance (p=0.11). A post hoc analysis of the data using monthly seizure counts, the negative binomial distribution and adjusting for the clinical covariates did achieve statistical significance (model-based p=0.0056; empirical p=0.012).

Sponsor's post hoc model used three modifications to achieve statistical significance
The sponsor's post hoc model used three modifications (monthly seizure counts, the negative binomial and adjusting for the clinical covariates) from the pre-specified model. The post hoc model achieved statistical significance (p = 0.012).

However, the sponsor's post hoc modified model is only 1 out of several possible post hoc models that explore combinations of these 3 modifications. As shown in Figure 9 below, some achieve statistical significance while some do not. Using this notation, the sponsor's originally pre-specified model was model 1 while their modified post hoc model is model 8. As seen, while the estimated treatment effect (in terms of the relative risk reduction in seizure count for Treatment vs. sham) is fairly consistent, the width of the confidence interval (and thus statistical significance) is highly dependent on the specific form of the GEE model used, as well as standard error estimation methods (empirical vs. model-based).

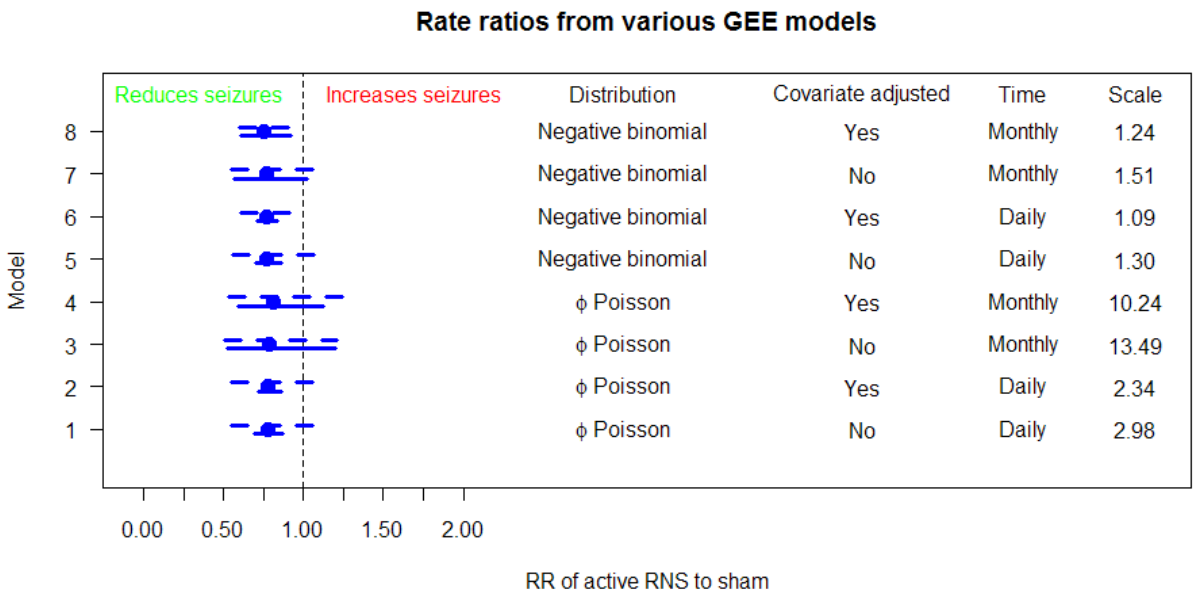


Figure 9. "Forest plot" Comparison of Alternative GEE Models

Circles denote relative risk reduction for active treatment relative to Sham; 95% confidence intervals are presented for model-based (solid) and empirical (dashed) horizontal lines. The relative risk reduction corresponds to the additional reduction in seizure frequency attributable to active stimulation relative to Sham stimulation; a value of 1 would suggest there is no additional benefit from active stimulation, while a value less than 1 or greater than 1 would indicate that active stimulation reduces or increases seizures relative to Sham stimulation. Model 1 represents the pre-specified analysis model, while model 8 represents the final post hoc analysis model.

As seen in the Table 41, based on the post hoc GEE analysis having all three modifications, the model predicts a percent change of seizure frequency from baseline in the Treatment group of -37.9% (95% confidence interval: -46.7%, -27.7%) versus -17.3% (-29.9%, -2.3%) in the Sham group.

Table 41. Estimates of seizure frequency percent change from the modified GEE model: over the entire Blinded Evaluation Period

	Parameter Estimate (log scale)[1]	Ratio of Seizure Frequency (Blinded Evaluation Period vs. Pre-Implant Period)[2]	Percent Change from Pre-Implant Period[3] [95% confidence interval]
Treatment	-0.4771	0.621	-37.9% [-46.7%, -27.7%]
Sham	-0.1898	0.827	-17.3% [-29.9%, -2.3%]

[1] The parameter estimate (β) for the Sham group is the coefficient for Time (β_1). The parameter estimate for the Treatment group is the coefficient for Time + the coefficient for Group-by-Time ($\beta_1 + \beta_2$).

[2] The ratio of seizure frequency (natural scale) is given by e^{1}.

[3] The percent change is given by $(e^{\beta} -1)*100\%$.

The sponsor's selected post hoc model is one of several plausible models

There are a total of 8 GEE models with combinations of 3 post hoc modifications (Poisson vs. negative binomial; covariates adjusted or not; daily vs. monthly). Some achieve statistical significance, and some do not. The statistical significance of a model is sensitive to its specific form as well as its standard error estimation method (empirical vs. model-based).

The panel will be asked to discuss the reliance upon post hoc analyses out of several plausible models to demonstrate statistical significance.

A post hoc bootstrap analysis was conducted to explore the robustness of the statistical significance of the estimated treatment effect from the post hoc GEE analysis model. This analysis randomly re-sampled the total study population of 191 subjects, randomly assigning 97 subjects to Active treatment and 94 to Sham-treatment. This was repeated to generate 2500 simulated datasets. This approach simulates clinical trial data under the null hypothesis of no treatment effect, so that the expected treatment effect would be zero. The post hoc GEE model was then applied to the resulting datasets. The results suggest that there the likelihood of observing by chance a treatment effect of the magnitude observed in the post hoc model is approximately 2%.

9.4.4. Mean and Median Seizure Frequency Analysis

The mean and median seizure frequencies are shown in Figures 4 and 5 above. Following implant of the device and prior to initiation of stimulation, there is a reduction in seizure frequency in terms of mean or median. For subjects in the Treatment group, initiation of stimulation does not result in a change of seizure frequency as compared to post implant. In contrast, mean seizure frequency for subjects in the Sham group appears to return baseline during the last month of the blinded phase. However, the range of the number of seizures experienced during month 4-5 is 0 to 799. Furthermore, the median reduction in seizure frequency in the Sham group does not support a return to baseline. Thus, there was an initial "surgical effect", wherein active stimulation does not appear to confer any benefit beyond an initial improvement following the surgical placement of the device. This initial improvement does not appear to last through the blinded phase.

The return to baseline observed in Sham-treated subjects by months 4-5 appears to be driven primarily by 2 highly influential Sham-treated subjects [redacted] and [redacted]. These 2 subjects are among those with the highest number of seizure counts at baseline and do not behave similarly to other Sham-subjects with extremely high seizure counts, as their seizure frequency increased by the end of the BEP, whereas other Sham-treated subjects with >84 seizures per month decreased. Excluding these 2 subjects has a significant impact on the Sham-treated means; not only for the most severe group (Figure 10), but also for the overall Sham-treated group (Figure 11). Excluding these 2 subjects from the mean seizure analysis effectively eliminates the observed return to baseline in Sham-treated subjects. Section 9.4.6 discusses these 2 highly influential Sham-treated subjects in more detail.

"Surgical Effect"

All subjects (who would later be randomized into treatment and sham groups) experienced a decrease in seizure counts following implant but prior to initiation of stimulation.

The panel will be asked to discuss the apparent "surgical effect" and its effect on the overall treatment effect of the device.

9.4.5. Stratification by Baseline Number of Seizures

Considering that the median reduction does not demonstrate a return to baseline and that the range of seizures in the Sham group was 0 to 799 during month 4-5 as compared to 3-338 during the pre-implant period at baseline, CDRH stratified the data by the baseline number of seizures. This post hoc analysis was conducted to assess an underlying assumption of the GEE model, which is that the overall treatment effect applies equally to all subjects, regardless of baseline seizure count. Subjects were classified into 1 of 4 categories based upon the average number of seizures experienced per month at baseline: 0-28, 29-56, 57-84, >84; these categorizations correspond to <1, 1-2, 2-3, >3 seizures per day on average. The number of subjects in each category and the mean number of seizures at baseline, are provided in Table 42 below. Table 43 presents the relative treatment effect overall, as well as by baseline category. These results are presented graphically in Figure 10 below. The results suggest that the magnitude of the overall treatment effect may not be uniform, but may be larger in the categories with larger seizure counts at baseline. These results were similar when repeated by quartile, suggesting that the effect is not an artifact of the cut-points used for grouping (results not shown).

Table 42. Sham and Treatment by categorization of number of seizures at baseline

	Sham				Treatment			
	Pre		Post		Pre		Post	
Baseline Frequency	n	Mean	n	Mean	n	Mean	N	Mean
0-28 seizures per month	69	9.6	66*	8.0	71	8.3	69*	6.5
29-56 seizures per month	12	37.0	12	32.3	8	39.3	8	24.3
57-84 seizures per month	6	71.3	6	65.0	6	73.1	6	52.3
>84 seizures per month	7	249.2	7	274.3	12	159.1	12	90.1

*5 subjects (3 Sham, 2 Treatment) had missing data for the last month of the BEP period

**Results after excluding 2 sham subjects ([redacted]).

Table 43. Relative treatment effect by categorization of number of seizures at baseline

Baseline Frequency (monthly seizure count)	Relative risk*	Empirical		Model-based	
		95% CI	p-value	95% CI	p-value
All subjects	0.75	0.60 , 0.94	0.0123	0.61 , 0.92	0.0056
0-28 seizures per month	0.84	0.65 , 1.07	0.1551	0.69 , 1.02	0.0719
29-56 seizures per month	0.98	0.56 , 1.70	0.9423	0.66 , 1.46	0.9199

Baseline Frequency (monthly seizure count)	Relative risk*	Empirical		Model-based	
		95% CI	p-value	95% CI	p-value
57-84 seizures per month	0.77	0.53 , 1.12	0.1660	0.59 , 1.00	0.0529
>84 seizures per month	0.50	0.28 , 0.89	0.0190	0.32 , 0.78	0.0019
0-84 seizures per month	0.86	0.70 , 1.05	0.1298	0.73 , 1.01	0.0624

* Regardless of using empirical or model-based methods, the estimated treatment effect size is identical.

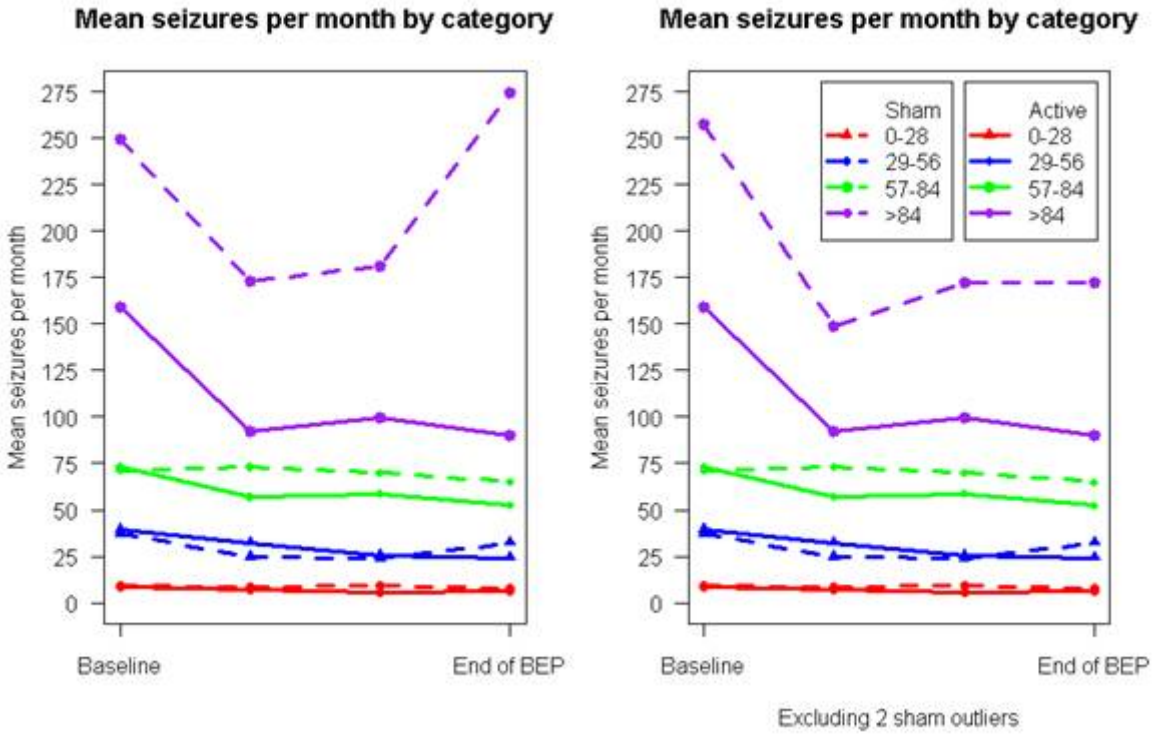


Figure 10. Overall mean monthly seizure count by treatment group and baseline seizure frequency category, Left: including all subjects, Right: excluding 2 Sham subjects - [redacted].

The majority of observed benefit occurred in subjects with more than 84 seizures per month at baseline (approximately 9% of the subjects)

An underlying assumption of the GEE model is that the treatment effect is roughly similar for all subjects regardless of their baseline seizure frequency. However, a post hoc analysis by baseline seizure frequency category reveals that the majority of the observed benefit occurred in subjects with more than 84 seizures per month at baseline (approximately 9% of the subjects).

The panel will be asked to discuss the effect of the variable baseline seizure frequencies on the overall treatment effect of the device.

9.4.6. Influence of 2 Highly Influential Sham Subjects

As seen in the figures below, if the 2 highly influential Sham-treated subjects are removed, the return to baseline effect is ameliorated in both the overall results and the results by baseline categorization. If the post hoc analysis model (GEE with negative binomial, grouped by month, adjusted for clinical covariates) is repeated but these 2 subjects excluded, the magnitude of the relative treatment effect is reduced. Table 44 shows the estimates of seizure frequency percent change from the modified GEE model based upon all subjects or excluding the 2 highly influential Sham-treated subjects.

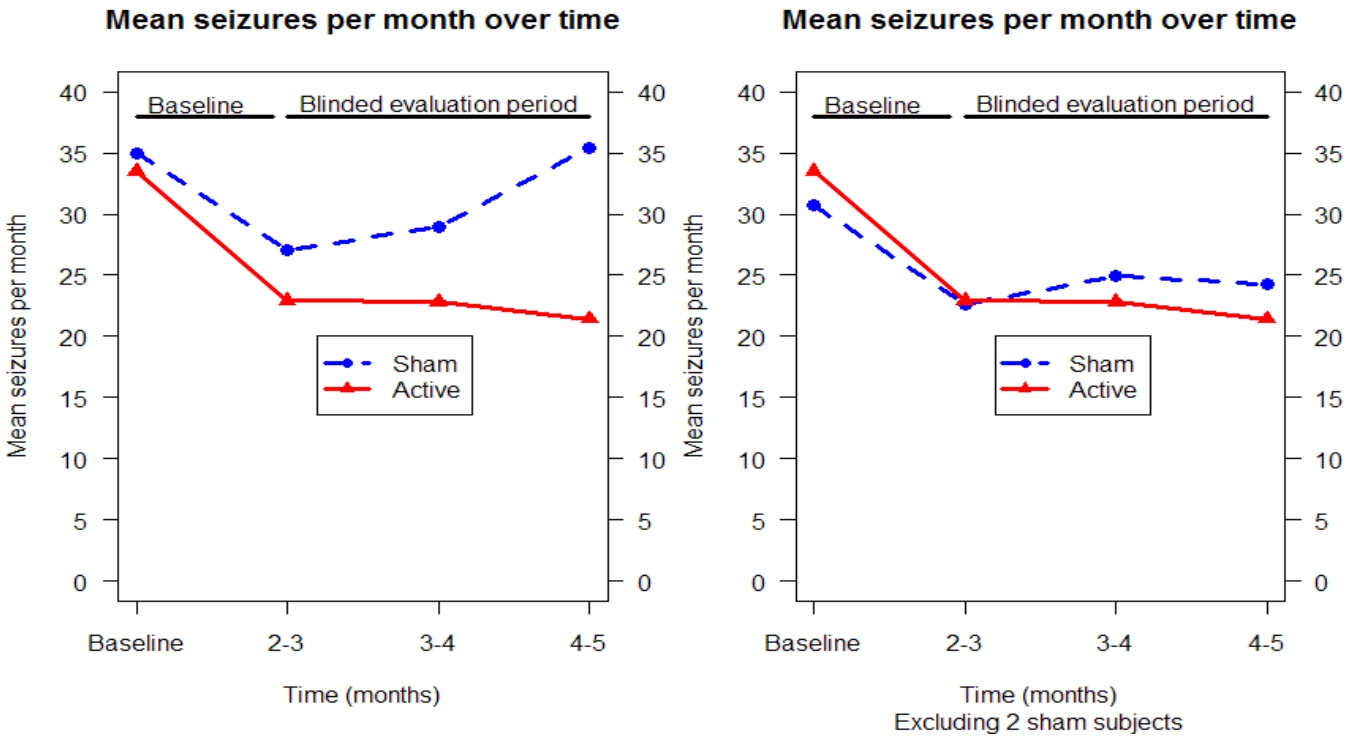


Figure 11 a and b. Overall mean monthly seizure count by treatment group, Left: including all subjects, Right: excluding 2 Sham subjects - [redacted]

Table 44. Estimates of seizure frequency percent change from the modified GEE model based upon all subjects or excluding the 2 highly influential Sham-treated subjects

	Treatment	Sham	p-value (empirical)	p-value (model-based)
All subjects	37.9%	17.3%	0.012	0.006
Excluding 2 Sham-treated subjects	36.9%	23.3%	0.080	0.026

To put the model-predicted percent change from baseline into perspective, Table 45 below presents the mean number of seizures the model would predict a typical Treated and Sham subjects would experience at the end of the Blinded Evaluation Period; 2 hypothetical baseline number of seizures are provided: 30 and 300.

Table 45. Model-predicted change from baseline to end of the Blinded Evaluation Period for Treatment and Sham subjects, based on either the full model with all subjects or excluding the 2 highly influential Sham-treated subjects. Two representative baseline seizure frequencies per month are provided: 300 and 30.

Mean Seizure Frequency per Month at baseline	Model-predicted mean post treatment					
	All subjects			Excluding 2 highly influential Sham subjects		
	Treatment	Sham	Difference	Treatment	Sham	Difference
300	186	248	62	189	230	41
30	19	25	6	19	23	4

Figure 12 below shows the response over time for each subject for Treatment subjects and Sham subjects (2 highly influential Sham-treated subjects [redacted] are colored differently for identification).

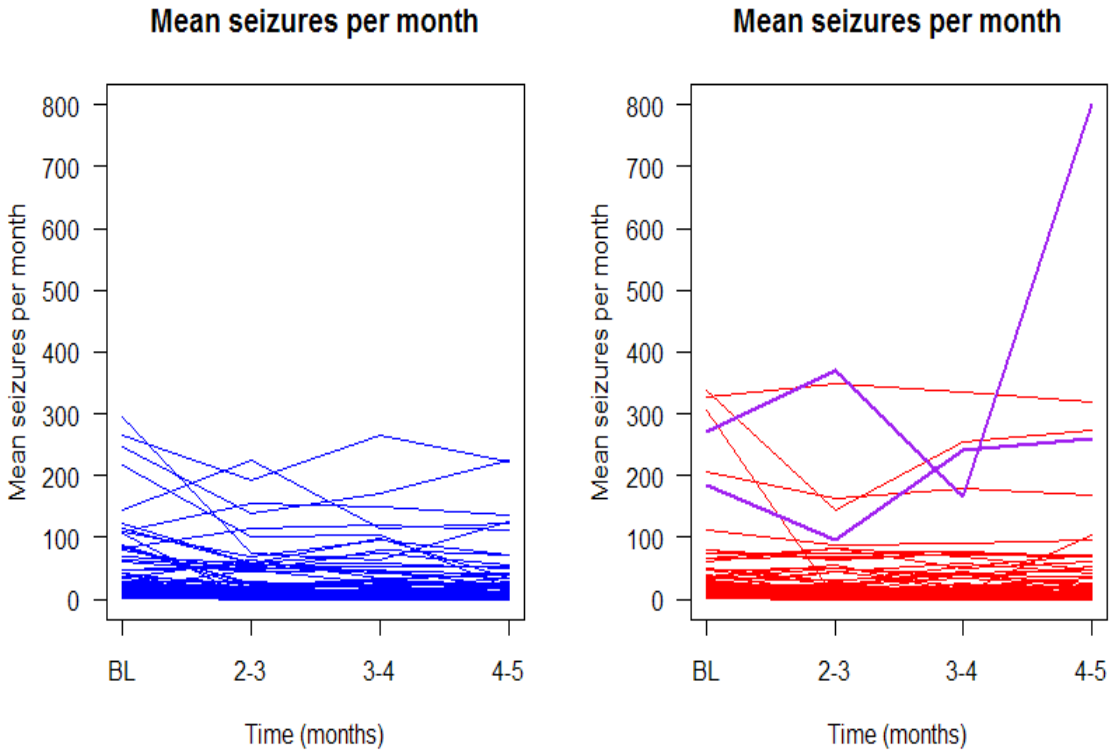


Figure 12 a and b. Response over time for each subject: a: Treatment subjects, b: Sham-treated subjects (2 highly influential Sham-treated subjects [redacted] are colored differently for identification).

These 2 subjects are highly influential on the observed treatment effect. When model fit diagnostics are examined, these 2 subjects have the highest cluster-level Cook's distance statistics, which measures the effect of deleting these 2 data points on the treatment effect estimate (see Figure 13 below; these 2 subjects are denoted with red triangles; all others are marked with blue dots). The subject with the next highest Cook's distance, [redacted], had the fourth highest baseline seizure counts in the Treatment group. For completeness, the proposed revised model was run excluding this subject as well as the 2 control subjects above – the results remain statistically non-significant using both the empirical and model-based standard error

(results not shown). In the GEE context, influence means that if the model is run including these subjects and again excluding them and the treatment effect estimates compared, the estimates are different. This indicates that the magnitude of the treatment effect is highly sensitive to these 2 subjects.

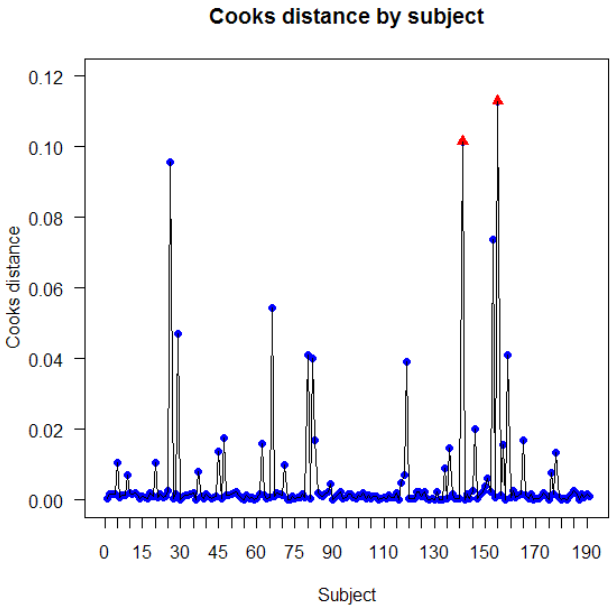


Figure 13. Cook's distance model fit statistic from sponsor's post hoc GEE model. The 2 highly-influential Sham-treated subjects are plotted with red triangles; all other subjects are plotted with blue dots.

While these subgroup analyses are *post hoc* and the reduced sample sizes do not assure adequate power to detect statistical significance, these analyses raise 2 concerns regarding the robustness of the observed treatment effect from the sponsor's post hoc GEE model. First, the post hoc analysis by baseline seizure frequency category shows that the majority of the observed benefit appears to be attributed to those subjects with >84 seizures per month at baseline. This suggests a violation of an underlying assumption of the GEE model that the effect is roughly similar for all subjects. Second, the means over time are very sensitive to 2 highly influential Sham-treated subjects with extremely high baseline seizure counts. These 2 subjects have a different response profile over time than other sham-treated subjects (worsen from baseline to end of BEP). Excluding these 2 highly influential subjects is statistically significant only for the model-based standard error, not the empirical. As referenced above and in the statistical Appendix, CDRH believes that the empirical standard error approach is preferable for its robustness, although expressed a preference for the model-based approach for the pre-specified analysis model.

Two highly influential Sham-treated subjects' impact on the size of the observed treatment effect

The response profile of 2 Sham subjects, who had extremely high seizure counts at baseline, is distinctly different than other Sham subjects. The outcome of these 2 subjects is so heavily influential that once these 2 subjects are removed, the mean response of the Sham group no longer returns to the baseline at the end of the blinded period, i.e. the surgical effect remains throughout the blinded period. As a result, the relative treatment effect size is reduced.

The panel will be asked to discuss the impact of the 2 highly influential Sham-treated subjects on the overall treatment effect of the device.

9.4.7. Post-Hoc Primary Effectiveness Endpoint Analysis by Month

The sponsor provided a post hoc analysis of seizure reduction by month. If all subjects are included, by the third month of the Blinded Evaluation Period, the Treatment group has experienced a 41.5% reduction in seizures from baseline, compared to a 9.4% reduction in seizures in the Sham group. However, if the two highly influential Sham-treated subjects [redacted]) are excluded the difference is 40.1% versus 22.9% for the Treatment and Sham groups, respectively.

The panel will be asked to discuss the effect of the month-to-month variation in seizure frequency (i.e., the post-hoc comparison of the Treatment ad Sham groups using only data from a particular month may introduce additional variability relative to the pre-specified analysis based upon the full 3 month BEP) on the overall treatment effect of the device.

9.4.8. Per Protocol Effectiveness Analysis

There were 9 subjects with protocol deviations that led to exclusion from the Per-Protocol analysis. Seven subjects were identified by persons blinded to the treatment allocation and before any analyses were conducted. Two were identified after the initial analysis when it was determined that there were clinically significant changes in antiepileptic medications. When the sponsor's post hoc GEE model was run on the per protocol population excluding these 9 subjects, the results were similar to the full dataset (empirical p=0.0267, model-based p=0.0098).

9.5. Secondary and Supportive Effectiveness Endpoints

The secondary effectiveness analyses were intended to support the primary effectiveness endpoint. Pre-specified secondary effectiveness endpoints were the responder rate, change in mean seizure frequency, proportion of seizure-free days, and self-reported seizure severity according to the Liverpool Seizure Severity Scale inventory. The median percent change in seizures was also compared. Results are provided in Table 46 below. None of secondary endpoints achieved statistical significance. Note that with the exception of the responder rate comparison, which was used to determine the trial's sample size, the protocol did not evaluate the trial's power to detect a statistically significant difference for the secondary outcomes.

The sponsor will be asked to discuss the effect of the secondary endpoint results on the overall treatment effect of the device.

Table 46. Pivotal Trial - Secondary Effectiveness Endpoints over the Entire Blinded Evaluation Period and over Month 3

Effectiveness Endpoint	Entire Blinded Evaluation Period		Month 3 of Blinded Evaluation Period	
	Treatment	Sham	Treatment	Sham
50% Responder Rate	29%	27%	34%	30%
Change in Mean Seizure Frequency	-11.4	-5.3	-12.7	-0.3
% Change in Days with Seizures[1]	-19%	-18%	-27%	-16%
Median % Change in Seizures	-28%	-19%	-34%	-19%

[1] Significant difference between Treatment and Sham at month 3 (p = 0.048 per t-test of proportion of days with seizures)

9.5.1. Responder Rates

Responder rate was defined as the proportion of subjects who experienced a 50% or greater reduction in mean disabling seizure frequency compared to the 12-week baseline period. Table 47 provides the responder rates over the blinded evaluation period. The sample size was based on the expectation of a 40% responder rate in the treatment group and a 20% responder rate in the Sham group. However, the responder rate in the Treatment group was 29% and 27% in the Sham group which was not statistically significant (p=0.727). Table 47 also provides responder rates over the individual months of the blinded evaluation period.

Failed to attain statistical significance for the responder rate, for which the study was sized
The study's sample size calculation aimed to detect a significant difference in responder rate of 50% seizure reduction, not the primary continuous endpoint in the pre-specified GEE model. All things equal, analysis of continuous endpoint tends to offer more power than binary endpoints such as responder rate. In this case, although the study was designed based on the secondary endpoint of responder rate, it was not met.

Table 47. Pivotal Effectiveness – Secondary Analysis: Responder Rates during the Blinded Evaluation Period, Treatment vs. Sham

Blinded Evaluation Period	Treatment % Responders (n/N[2])	Sham % Responders (n/N[2])	P-value[1]
Entire Blinded Evaluation Period	29% (28/96)	27% (25/93)	0.727
Month 2-3	34% (33/96)	39% (36/93)	0.536
Month 3-4	39% (37/95)	31% (28/90)	0.264
Month 4-5	34% (32/95)	30% (27/91)	0.557

[1] P-value per z-statistic.
[2] N represents the number of subjects for which any seizure data are available for that time period.

9.5.2. Seizure-Free Days

Table 48 compares the mean numbers of seizure-free days (per 28 days) during the 12-week baseline period before implantation and during the 12-week blinded evaluation period. In the

treatment group, there was a mean of 10.7 days with seizures per 28 days before implantation and 8.5 days with seizures per 28 days during the blinded evaluation period, a change of -18.9%. In the Sham group, the mean number of days on which a seizure occurred changed from 10.6 days with seizures/ 28 days before implantation to 8.9 days with seizures/ 28 days during the blinded evaluation period, a change of -18.3%. Table 48 also provides the mean number of days with seizures per 28 days for the individual months of the blinded evaluation period.

Table 48. Pivotal Effectiveness – Secondary Analysis: Change in Days with Seizures during the Blinded Evaluation Period by Month, Treatment vs. Sham

Period	Treatment				Sham			
	N	Mean Number of Days with Seizures (per 28 days)		%Change	N	Mean Number of Days with Seizures (per 28 days)		%Change
		Pre-Implant	Post-Implant			Pre-Implant	Post-Implant	
Blinded Evaluation Period	96	10.7	8.5	-18.9%	93	10.6	8.9	-18.3%
Month 2-3	96		8.9	-12.9%	93		8.8	-19.5%
Month 3-4	95		8.3	-25.0%	90		9.1	-15.7%
Month 4-5	95		7.9	-26.9%	91		9.2	-15.8%

9.5.3. Change in Mean Seizure Frequency

The change in mean seizure frequency was -11.4 seizures per month in the Treatment group and -5.3 in the Sham group; this between-groups change was not statistically significant (p=0.238) (Table 49).

Table 49. Pivotal Effectiveness – Secondary Analysis: Change in Mean Seizure Frequency during the Blinded Evaluation Period, Treatment vs. Sham Mean Frequency of Disabling Seizures (seizures/month)

	Treatment (N=96)[1] (Mean ± SD)	Sham (N=93)[1] (Mean ± SD)	Across Group p-value[2]
Pre-Implant	33.8 ± 57.0	35.2 ± 67.4	
Blinded Evaluation	22.4 ± 39.5	29.9 ± 66.5	--
Change	-11.4 ± 32.1	-5.3 ± 39.1	0.238

[1] Includes subjects who have at least one day of data in both the Pre-Implant and Blinded Evaluation Periods

[2] By two-sample t-test

9.5.4. Change in the Liverpool Seizure Severity Inventory

Table 50 compares the Liverpool Seizure Severity Scores for the 12-week baseline period before implantation and the 12-week blinded evaluation period. In the treatment group, the scores changed from 43.8 before implantation to 39.1 during the blinded evaluation period, a change of -4.7. In the Sham group, the scores changed from 45.1 before implantation to 39.2 during the blinded evaluation period, a change of -5.9. The difference between groups was not statistically significant (p=0.574).

Table 50. Pivotal Effectiveness – Secondary Analysis: Mean Change in Liverpool Seizure Severity Scores During the Blinded Evaluation Period, Treatment vs. Sham

Period	Liverpool Scaled[1] Score		
	Treatment (N = 95)[2] (mean ± SD)	Sham (N = 93)[2] (mean ± SD)	Across Group p-value[3]
Pre-Implant	43.817 +/- 18.111	45.092 +/- 18.691	--
Blinded Evaluation	39.110 +/- 19.689	39.228 +/- 19.358	
Change	-4.707 +/- 12.911	-5.864 +/- 15.178	0.574

[1] Scaled score (ICTAL) per Scott-Lennox et al., 2001.
[2] Includes subjects who have at least one observation in both the Pre-Implant and Blinded Evaluation Periods.
[3] By two-sample t-test.

9.5.5. Median Percent Change in Seizures

The median percent change in seizures was -28% in the Treatment and -19% in the Sham.

9.6. Additional Analyses

9.6.1. Percent Reduction by Deciles

The pre-defined responder rate definition was a 50% improvement from baseline. As a sensitivity analysis, the response rate was examined by decile from 10% through 90%; none of the categorizations showed a statistically significant difference between the Treatment and Sham groups (Table 51).

Table 51. Pivotal Effectiveness – Secondary Analysis: Seizure Frequencey Percent Reduction, Response by Decile (Blinded Evaluation Period vs. Pre-Implant Period)

Group	N	% (n/N)								
		10%	20%	30%	40%	50%	60%	70%	80%	90%
Treatment	96	71% (68/96)	60% (58/96)	46% (44/96)	39% (37/96)	29% (28/96)	24% (23/96)	16% (15/96)	8% (8/96)	5% (5/96)
Sham	93	59% (55/93)	49% (46/93)	42% (39/93)	34% (32/93)	27% (25/93)	20% (19/93)	12% (11/93)	8% (7/93)	4% (4/93)

9.6.2. Subset Effectiveness Analyses

Subset analyses were pre-specified in the investigational plan to evaluate whether specific clinical characteristics (seizure onset zone, number of seizure foci, prior surgery for epilepsy, and antiepileptic drug (AED) changes) affected the clinical outcome. These subset analyses were not powered to show effectiveness.

9.6.2.1. Seizure Onset Zone

An exploratory analysis was performed to assess whether the treatment is consistent across seizure onset zone (mesial temporal lobe only or other regions). Ninety five (95) subjects, 48 Treatment and 47 Sham, had mesial temporal onset. At baseline, the range of seizures in the active group was 3 to 216.67 and in the sham group 3.33 to 79.33. During the Blinded Evaluation Period, the responder rate for subjects with mesial temporal lobe onset in the Treatment group was 33% (16/48) and 26% (12/47) for subjects in the Sham group. Ninety six

subjects, 49 treatment and 47 sham, had seizure onset in other regions (i.e., not mesial temporal onset). At baseline, the range of seizures in the active group was 3 to 294.67 and in the sham group 3 to 338. During the Blinded Evaluation Period, the responder rate for those in the Treatment group was 24% (12/49) and 28% (13/47) for subjects in the Sham group. See Table 52 below.

Table 52. Subset Analyses: Post hoc Responder Analysis of Mesial Temporal Onset Seizures and Other Onset Seizures

	Treatment Pre-implant	Treatment Post-implant	Sham Pre-implant	Sham Post-implant	Difference (Treatment – Sham)
Mesial Temporal Onset (N=95)					
Range	(3, 216.67)	(0, 93)	(3.33, 79.33)	(0, 78)	--
Responders	--	33% (16/48)	--	26% (12/47)	7%
Other Onset (N=96)					
Range	(3, 294.67)	(0, 247)	(3,338)	(0, 799)	
Responders	-	24% (12/49)	-	28% (13/47)	-4%

Range of average baseline seizure frequency per month
Responder based on at least a 50% improvement from baseline

9.6.2.2. Number of Seizure Foci

Eighty five (85) subjects, 49 Treatment and 36 Sham, had one seizure focus. At baseline, the range of seizures in the Treatment group was 3 to 294.67 and in the Sham group 3.33 to 338. During the Blinded Evaluation Period, the responder rate for those in the Treatment group was 31% (15/49) and 28% (10/36) for subjects in the Sham group. One hundred six (106) subjects, 48 Treatment and 58 Sham, had two seizure foci. At baseline, the range of seizures in the Treatment group was 3 to 88.33 and in the Sham group 3 to 185. During the Blinded Evaluation Period, the responder rate for those in the Treatment group was 27% (13/48) and 26% (15/58) for subjects in the Sham group. See Table 53 below.

Table 53. Subset Analyses: Post hoc Responder Analysis by Number of Seizure Foci

	Treatment Pre-implant	Treatment Post-implant	Sham Pre-implant	Sham Post-implant	Difference (Treatment – Sham)
One Seizure Focus (N=85)					
Range	(3, 294.67)	(0, 247)	(3.33,338)	(0, 799)	--
Responders	-	31 % (15/49)	-	28% (10/36)	3%
Two Foci (N=106)					
Range	(3, 88.33)	(0, 59)	(3, 185)	(0, 261)	
Responders	-	27% (13/48)	-	26% (15/58)	1%

Range of average baseline seizure frequency per month
Responder based on at least a 50% improvement from baseline

9.6.2.3. Prior Surgery

Sixty two (62) subjects, 34 Treatment and 28 Sham, had prior epilepsy surgery. At baseline, the range of seizures in the Treatment group was 3 to 294.67 and in the Sham group 3 to 338. During the Blinded Evaluation Period, the responder rate for those in the Treatment group was 24% (8/34) and 29% (8/28) for subjects in the Sham group. One hundred twenty nine (129) subjects, 63 Treatment and

66 Sham, did not have prior epilepsy surgery. At baseline, the range of seizures in the Treatment group was 3 to 266 and in the Sham group 3.33 to 207. During the Blinded Evaluation Period, the responder rate for those in the Treatment group was 32% (20/63) and 26% (17/66) for subjects in the Sham group. See Table 54 below.

Table 54. Subset Analyses: Post hoc Responder Analysis by Resection and No Prior Resection

	Treatment Pre-implant	Treatment Post-implant	Sham Pre-implant	Sham Post-implant	Difference (Treatment – Sham)
Prior Resection (N= 62)					
Range	(3, 294.67)	(0, 226)	(3, 338)	(0, 799)	--
Responders	-	24% (8/34)	-	29% (8/28)	-5%
No Prior Resection (N= 129)					
Range	(3, 266)	(0, 247)	(3.33, 207)	(0, 261)	
Responders	-	32% (20/63)	-	26% (17/66)	6%

Range of average baseline seizure frequency per month
Responder based on at least a 50% improvement from baseline

9.6.2.4. Changes in Antiepileptic Drugs

There were only 6 subjects who had changes in their AED treatment regimen, 3 subjects had changes in the Pre-Implant Period and 3 subjects had changes in AEDs in the Blinded Evaluation Period. The 6 subjects who had AED changes were excluded from analyses of the Per-Protocol Population. Results of the Per-Protocol analysis indicate that the Treatment Effect remains significant with the subjects who had significant protocol deviations (including AED changes) removed from the analysis (p = 0.027).

The panel will be asked there is a subgroup for which there is a reasonable assurance that the device is safe and effective (e.g., specific seizure type, specific location of seizure foci, number of foci, baseline seizure count, and history of prior surgery).

9.6.3. Awareness of Side Effects

An analysis was performed to examine whether awareness of side effects influenced the Treatment Effect. At the end of the Blinded Evaluation Period (20 weeks post-implant), subjects were asked whether they thought they had been receiving stimulation therapy and why. Subjects were stratified into two subsets based on blinding assessment; subjects who had reported "awareness of side effects" versus those who did not report an "awareness of side effects".

Nine subjects (5%) thought they were receiving stimulation therapy because of "awareness of side effects." Eight of these 9 subjects were receiving stimulation; the other one was in the Sham group. The primary post-hoc GEE analysis repeated excluding these 9 subjects shows that the treatment effect remains significant (p=0.015).

9.6.4. Analysis of Seizure Subtypes

Additional analyses were pre-specified on seizure subtypes, i.e. simple partial motor seizures, complex partial seizures, and secondarily generalized tonic-clonic seizures. As seen in Table 55, there were no significant differences in Pre-Implant seizure frequency for any of the seizure

subtypes between the Treatment and Sham groups. However, the largest change is evident in simple partial motor seizures subtypes, but not in the other seizure subtypes.

Table 55. Pivotal Effectiveness – Seizure Subtype Analysis: Blinded Evaluation Period: Change in Mean Seizure Frequency, Treatment vs. Sham

Seizure Type, Period	Treatment (N=96) [1] (mean +/-SD, seizures/day)	Sham (N=93) [1] (mean +/-SD, seizures/day)	P-value[2]
Simple Partial – Motor			
Pre-Implant	13.738 +/- 45.091	16.797 +/- 59.134	
Blinded Evaluation	7.568 +/- 29.808	16.549 +/- 63.442	
Change	-6.170 +/- 24.939	-0.248 +/- 23.102	0.092
Complex Partial Seizures			
Pre-Implant	17.880 +/- 38.927	13.740 +/- 33.382	
Blinded Evaluation	12.606 +/- 26.128	9.264 +/- 15.745	
Change	-5.273 +/- 19.594	-4.476 +/- 32.787	0.839
Generalized Tonic-Clonic			
Pre-Implant	2.181 +/- 7.126	4.651 +/- 18.358	
Blinded Evaluation	2.188 +/- 6.339	4.081 +/- 15.916	
Change	0.007 +/- 3.606	-0.570 +/- 3.565	0.270

[1] Includes subjects who have at least one day of data in both the Pre-Implant and Blinded Evaluation Periods.

[2] p-value per 2-sample t-test

9.6.5. Pivotal – Long-Term (Open Label) Effectiveness

Subjects entered the open label phase of the study at 5 months (20 weeks) post-implant. At the 20-Week visit, subjects in the Sham group were able to receive responsive stimulation for the first time. During the open label phase, subjects knew they were receiving active stimulation, were able to modify their AEDs, and there were missing data. There may also be regression to the mean over time. All of these factors, combined with an untreated group for comparison, may confound the interpretation of the open label data.

As seen in Table 56 below, subjects in the Sham group had a statistically significant reduction in seizures during months 6 to 9 of the Open Label Evaluation Period relative to their Pre-Implant Period ($p = 0.04$). However, the reduction in seizure frequency averaged over months 6 to 9 of the Open Label Evaluation Period compared to the average during the Blinded Evaluation Period is not significantly different ($p = 0.39$).

Figure 14 provides a graphical representation of the mean change in seizure frequency for the Sham group from pre-implant through the 9 month visit. The reduction in seizures following the initiation of stimulation through month 9 is similar to that post implant, i.e. prior to initiation of stimulation.

The panel will be asked to discuss the use of open label data to make conclusions regarding the treatment effect of the device.

Table 56. Pivotal Effectiveness – Open Label: Change in Mean Seizure Frequency, Open Label Weeks 24-36 vs. Pre-Implant and Blinded Evaluation Periods, Sham Group

Time Period	Seizure Frequency[1] (mean ± SD, seizures/month)	
	Open Label to Pre-Implant Comparison (N = 91)	Open Label to Blinded Evaluation Comparison (N = 91)
Pre-Implant	35.725 ± 68.037	--
Blinded Evaluation (Months 2-5)	--	30.442 ± 67.082
Open Label (Months 6-9)	27.964 ± 2.014	27.964 ± 62.014
Change	-7.761 ± 35.498	-2.478 ± 27.33
p-value[2]	0.04	0.39

[1] Calculations include those subjects who were randomized to the Sham group for the Blinded Evaluation Period and who had had the opportunity to complete the 36-week study appointment(s)

[2] p-value based on paired t-test.

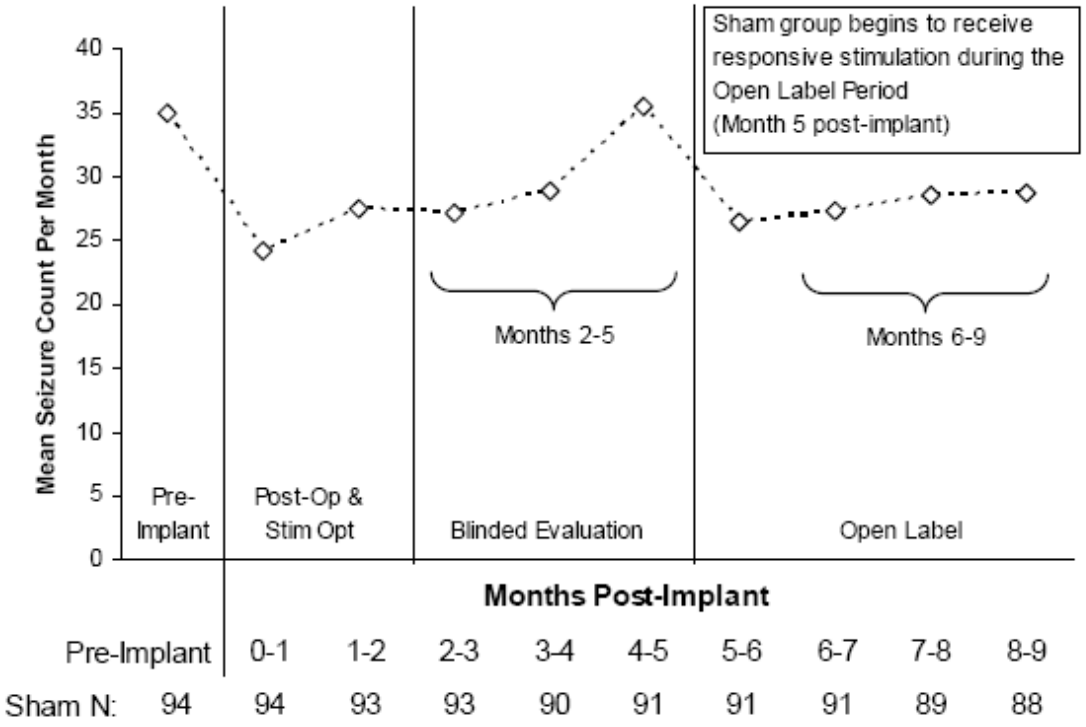
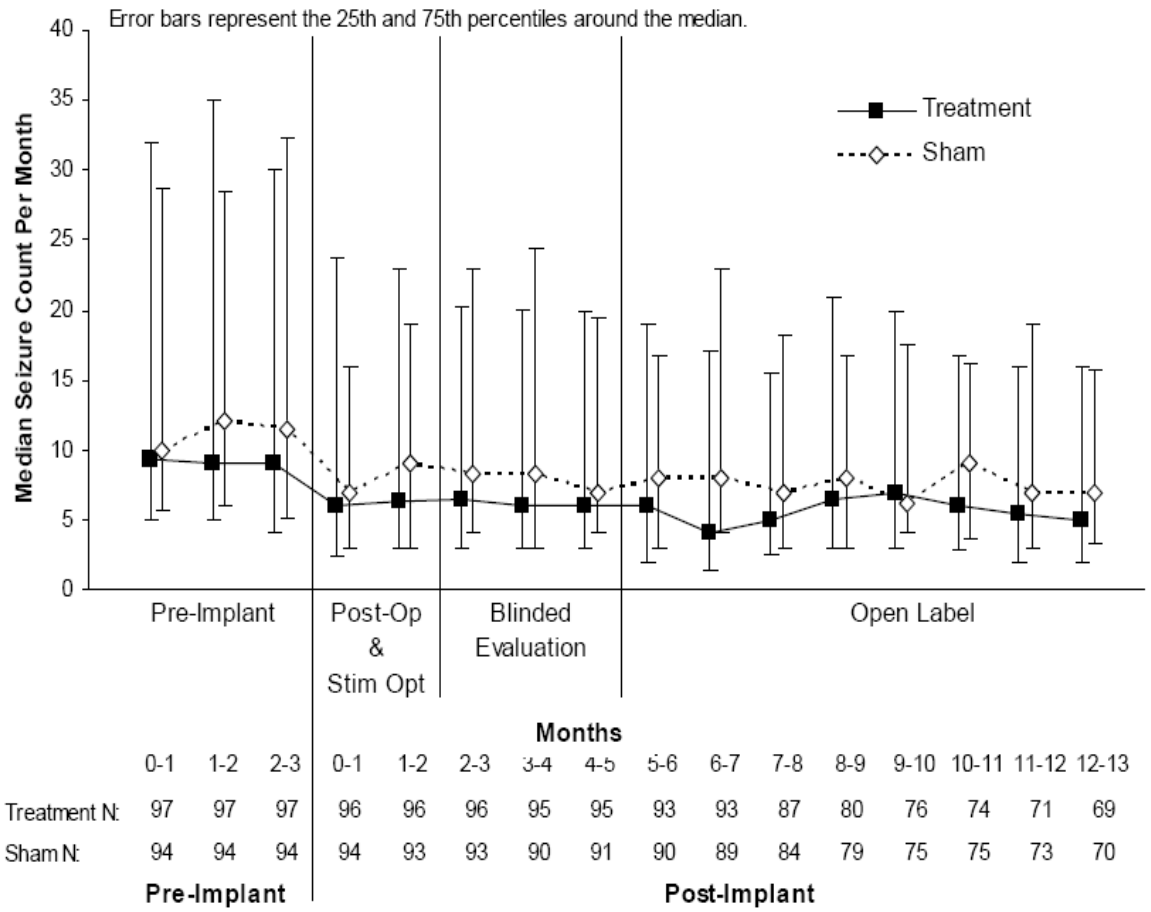


Figure 14. Pivotal Effectiveness – Mean Seizure Frequency by Month Pre-Implant Period through Month 9 Post-Implant (Sham Group) (Data as of June 4, 2010)

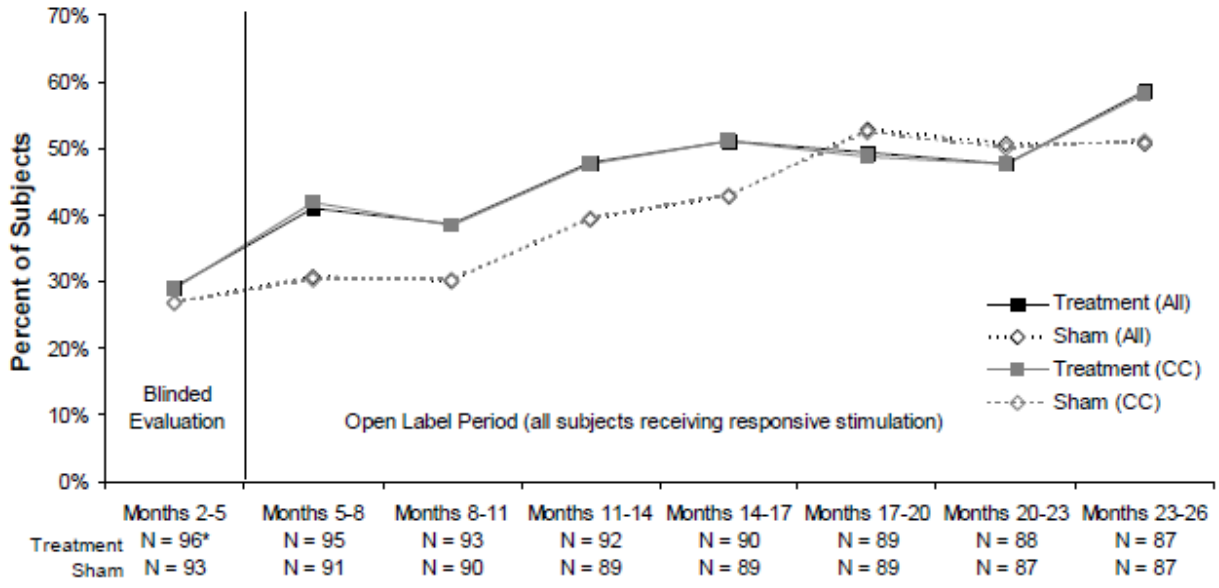
Figure 15 below represents the median seizure frequency per month from pre-implant to one year post implant for subjects in the Treatment and Sham groups. As can be seen, there is wide variation in seizure frequency.



Data as of October 16, 2009

Figure 15. Median Seizure Frequency per Month Pre-Implant Period through 1 Year Post-Implant

The responder rate for the subjects randomized to the Treatment and Sham groups during the Blinded Evaluation Period and for all subjects over the Open Label Evaluation Period are presented in Figure 16 below. Analyses in Figure 16 are presented for all subjects for whom any data were available (All) as well as for a constant cohort (CC; subjects for whom data were available for all periods). The responder analysis presented in Figure 16 represents the sponsor's, and the rate beyond 12 months have not been independently verified by FDA. As stated in Section 9.5.1 above, the sample size was based on the expectation of a 40% responder rate in the treatment group and a 20% responder rate in the Sham group. However, at the end of the Blinded Evaluation Period, the responder rate in the Treatment group was 29% and 27% in the Sham group which was not statistically significant (p=0.727). A gradual improvement was seen in the Open Label period.



Data as of May 12, 2011

Figure 16. Responder Rates: Blinded Evaluation Period through Open Label Period

Figure 17 below represents mean seizure counts up to two years post-implant in 3 month increments. The vertical lines represent the 95% confidence intervals for each time-point (lines are slightly offset from the data points to avoid overlap.) At the end of the blinded evaluation phase (BEP), all subjects received open label therapy; however, at the end of the BEP subjects were not told whether they had received active or sham stimulation during the BEP. It is important to note that the subjects who had been randomized to Sham have less of a mean seizure reduction and greater variability as compared to those randomized to Treatment. The analyses presented in Figure 17 represent the sponsor's and have not been independently verified by FDA.

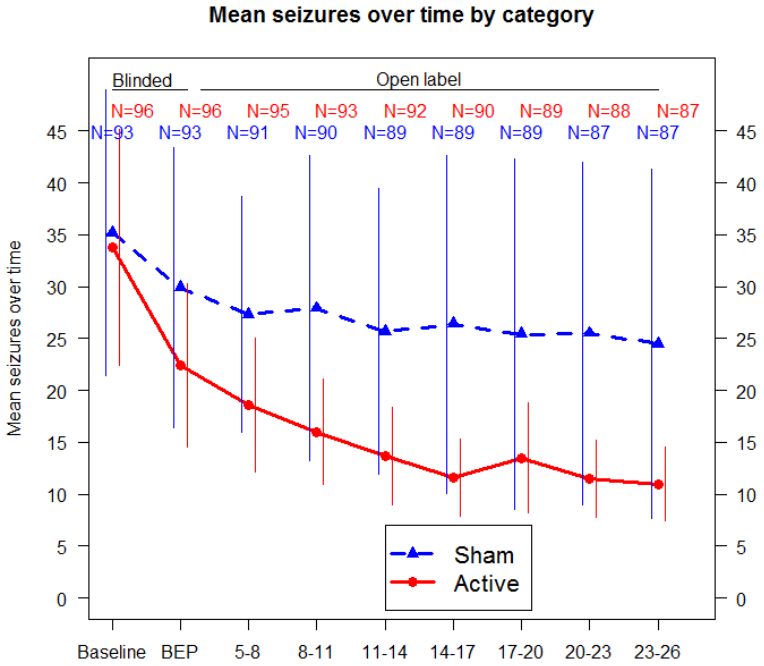


Figure 17. Change in Mean Seizure Frequency through Months 23-26

9.6.6. Quality of Life in Epilepsy Inventory

Quality of Life (QOL) was an additional assessment performed in the study. There was no difference between the Treatment and Sham groups on the overall QOLIE-89 or any of the subscales. A significant clinical improvement on the QOLIE assessment is defined as an improvement of 5 points or more. As seen in Table 57, 36.6% of subjects in the Treatment group and 39.1% of the subjects in the Sham group had at least a 5 point improvement. As seen in Table 58, at 1 and 2 years post-implant, 38% and 44% of subjects (respectively) experienced clinically significant improvements.

Table 57. Pivotal Study – Proportion of Subjects with ≥ 5 Point Improvement in Quality of Life Primary Scale Scores at 20 Weeks Relative to Baseline (per QOLIE-89 Scoring) Analysis includes subjects (N) with assessments available at both (pre- and post-implant) time points. Scores are calculated per QOLIE-89 scoring instructions.

Overall / Primary Scale	Treatment		Sham		Tx vs. Sham p-value (Fisher's Exact)
	N	% subjects improved (increase ≥ 5 points) (# subjects)	N	% subjects improved (increase ≥ 5 points) (# subjects)	
QOLIE-89 Overall Score	**93**	**36.6% (34)**	**87**	**39.1% (34)**	**0.760**
Health Perceptions	94	23.4% (22)	86	17.4% (15)	0.360
Overall Quality of Life	94	34% (32)	88	40.9% (36)	0.361
Physical Function	94	20.2% (19)	86	26.7% (23)	0.378
Role Limitation - Physical	94	46.8% (44)	86	39.5% (34)	0.368
Role Limitations - Emotional	94	36.2% (34)	86	30.2% (26)	0.432

Overall / Primary Scale	Treatment		Sham		Tx vs. Sham p-value (Fisher's Exact)
	N	% subjects improved (increase ≥ 5 points) (# subjects)	N	% subjects improved (increase ≥ 5 points) (# subjects)	
Pain	94	18.1% (17)	86	30.2% (26)	0.079
Work / Driving / Social Function	94	39.4% (37)	88	34.1% (30)	0.539
Energy / Fatigue	94	23.4% (22)	88	21.6% (19)	0.860
Emotional Well-Being	94	23.4% (22)	88	19.3% (17)	0.589
Attention/Concentration	94	41.5% (39)	88	42% (37)	1.000
Health Discouragement	94	36.2% (34)	86	27.9% (24)	0.266
Seizure Worry	94	38.3% (36)	88	36.4% (32)	0.878
Memory	94	31.9% (30)	86	33.7% (29)	0.874
Language	93	34.4% (32)	86	41.9% (36)	0.356
Medication Effects	94	34% (32)	88	29.5% (26)	0.529
Social Support	94	39.4% (37)	86	23.3% (20)	0.025
Social Isolation	94	24.5% (23)	85	21.2% (18)	0.722

A 5 point or greater increase in the overall or primary scale T-score relative to pre-implant is generally considered to be clinically significant (Norman et al. 2004; Norman et al. 2003). Data as of June 4, 2010.

Table 58. Pivotal Trial - QOLIE-89 Scales for which ≥ One Third of Subjects had a Clinically Significant Improvement at 1 or 2 years post-implant

	% (n/N) Subjects with Clinically Significant Improvement[1]	
	1 Year	2 Years
QOLIE-89 Overall Score	38% (63/166)	44% (68/154)
Seizure Worry	44% (73/167)	52% (81/155)
Attention / Concentration	46% (76/167)	43% (67/155)
Health Discouragement	40% (66/165)	43% (66/153)
Memory	41% (67/165)	43% (65/153)
Role Limitation-Physical	40% (66/165)	44% (68/153)
Language	40% (65/164)	42% (64/152)
Work/Driving/Social Function	35% (58/167)	43% (66/155)
Overall QOL	38% (63/167)	35% (54/155)
Medication Effects	35% (58/167)	35% (54/155)
Energy / Fatigue	35% (59/167)	32% (49/155)
Social Support	30% (50/165)	36% (55/153)

[1] Compared to pre-implant baseline. Data as of May 12, 2011.

9.6.7. Antiepileptic Drug (AED) Changes in the Open Label Period

As seen in the Figure 18 below, only 7.6% (14/183) subjects decreased their AEDs. In contrast, 21.9% (40/183) subjects increased their AEDs and 16.4% (30/183) had both an increase and decrease in AEDs. These changes in AEDs confound interpretation of the open label data.

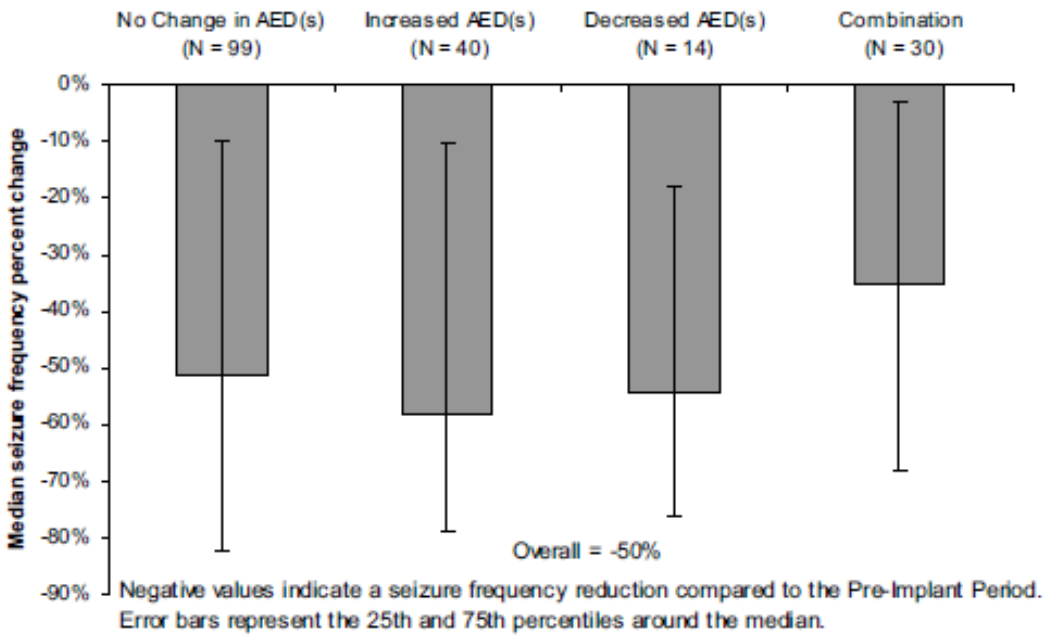


Figure 18. Median Seizure Frequency Percent Change and Change in Antiepileptic Medications in the Most Recent 3 Months of Open Label Period Relative to Pre-Implant Period (At least 3 months in the Open Label Period, N=183)

9.7. Clinical Conclusions

The RNS® System Pivotal Clinical Investigation was a multi-center, prospective, randomized, double-blind, sham-stimulation controlled pivotal study designed to assess the safety and effectiveness of the RNS® System for the proposed indications for use as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications.

9.7.1. Clinical Safety Conclusions

The FDA's safety assessment is based primarily on data collected through June 4, 2010. Data from the pivotal trial include a 4 month blinded period during which there was a concurrent comparator. To assess overall safety data from the largely open label feasibility trial are pooled with all safety data from the pivotal trial including the open label period to completion at 2 years after implantation. All subjects had completed follow-up to one year but not all subjects had completed the open label period of two years post-implantation in the pivotal trial by June 4, 2010. The Sponsor has provided additional open label data through May 12, 2011. Because safety data submitted since June 4, 2010 is incomplete and FDA has not called for a final complete data update safety beyond one year post-implantation cannot be assessed at this time.

The assessment of safety included analyses of the 191 implanted subjects in the pivotal study over the approximately 5 months from implantation to the end of the Blinded Evaluation Period and the overall safety population of 256 subjects (65 from the feasibility study and 191 from the pivotal study) through June 2, 2010. This included safety data on all subjects to one year post-implantation.

The study met the pre-specified primary safety endpoint with an acute (0-4 weeks post implantation) SAE rate of 12% [16.5% upper CB] and short-term chronic (0-12 weeks post-implantation) rate of 36% [42% upper CB]. However, there were 55 serious adverse events in 23 subjects that occurred in the combined treatment groups between implantation and the end of the blinded evaluation period at 20 weeks post-implantation. These included 7 subjects with implant site infection, 3 intracranial hemorrhages, 1 subject with bacterial meningitis and 4 subjects requiring device removal or revision. The most common non-serious adverse events were implant site pain and headache. Although there were no apparent differences in adverse events between the two treatment groups during the blinded phase, there was a suggestion of more injuries related to seizures in the active group as compared to the sham group. At 20 weeks post-implantation the overall risk of the device appears to be comparable to the risks of implantation of a deep brain stimulator or intracranial monitoring electrodes. Safety data on all subjects between 20 weeks and one year post-implantation did not raise any additional safety concerns.

During the entire pivotal study, including the open label evaluation period through June 4, 2010, there were 6 deaths due to SUDEP (SUDEP rate of 8.5/1000 patient years (95% confidence interval 3.8 to 18.9), two due to suicide and one due to lymphoma. Two additional deaths have occurred, one due to status epilepticus and one due to SUDEP. As of June 4, 2010, a total of 13 subjects had an intracranial hemorrhage, 98 subjects experienced 168 psychiatric events and 147 subjects experienced adverse events related to changes in seizures.

9.7.2. Clinical Effectiveness Conclusions

A total of 191 subjects in the pivotal trial were in the intent to treat analysis. 97 subjects were randomized to the Treatment group and 94 were randomized to the Sham group. The range of seizure frequency in the Treatment group preimplant was from 3 to 294.7 per month. The range of seizure frequencies in the Sham group was from 3 to 338 per month. During the blinded phase, the Treatment group's seizure frequencies ranged from 0 to 226.8 per month and the Sham group's from 0.3 to 446.6 per month. In addition, the seizure frequency range during month 4-5 in the Treatment group was 0.0 to 226.0 per month and in the Sham group was 0 to 799 per month.

The primary efficacy endpoint analysis was designed to establish superiority of the Treatment group to the Sham group in reducing the frequency of total disabling seizures (simple partial motor, complex partial and generalized tonic-clonic seizures) during the final 84 days of the Blinded Evaluation Period of the investigation. The pre-specified endpoint to be analyzed was the treatment (active or sham treatment) by time period (baseline or blinded evaluation period) interaction term in a Generalized Estimating Equation (GEE) longitudinal, Poisson regression model. The pre-specified dependent variable was the daily seizure frequency. The pivotal study was powered to demonstrate a difference of 20% in the responder rates between the active and sham groups, assuming at least a 40% responder rate in the active treatment group. The p-value using the pre-specified primary effectiveness model achieved statistical significance when using the model-based approach ($p<0.0001$), but not with the empirical standard error approach ($p=0.15$). Using the model based approach the percent change in seizure frequency from baseline in the Treatment group is -37.9% (95% CI: -46.7%, -27.7%) and in the Sham group is -17.3% (95% CI: -29.9%, -2.3%)

The sponsor determined (and CDRH agreed) that the pre-specified effectiveness analysis was not a good fit to the data and proposed a post-hoc GEE model that achieved statistical significance (model-based p=0.0056; empirical p = 0.012). FDA has identified several sources of uncertainty that could affect the interpretation of the results.

Although CDRH agreed that the pre-specified model was not appropriate, the sponsor's post hoc model is not the only appropriate model. There are several other plausible post hoc GEE analyses that do not achieve statistical significance. Other models result in treatment effects that are close to the sponsor's post hoc model, i.e. a reduction of 37.9% in monthly seizure frequency from baseline in the Treatment Group and 17.3% in the Sham Group. However, the variance in the results, and consequently the statistical significance, is affected by the GEE model used.

The apparent treatment effect is heavily influenced by a prominent "surgical effect" in that there was an initial improvement following implantation of the device and prior to the initiation of stimulation in both the Treatment and Sham groups. Subjects in the treatment group maintained this post-implant seizure reduction through the blinded evaluation period while the sham group showed a gradual return to the baseline seizure frequency. The gradual return to baseline in the sham group was driven by two subjects with very high seizure frequencies at the end of the blinded evaluation period compared to baseline. In a post hoc analysis conducted by CDRH, if these two highly influential subjects are removed then the "surgical effect" was also maintained in the Sham arm at the end of the blinded period. The overall relative estimated Treatment effect is heavily influenced by 2 highly influential Sham-treated subjects who experienced more seizures at the end of the blinded evaluation phase than at baseline.

The majority of enrolled subjects had complex partial seizures. A subgroup analysis of subjects with partial onset disabling simple partial motor seizures, complex partial seizures, and secondarily generalized seizures shows that the largest reduction in seizure frequency was in the disabling simple partial motor seizures subgroup.

There was no statistically significant difference between the Treatment and Sham groups on any of the secondary endpoints. In particular, the observed 50% responder rates in the Treatment and Sham group were 29% and 27%, respectively (p=0.73) for a placebo-adjusted treatment effect of 2%. The study was sized by assuming a responder rate for the Treatment group of 40% and Sham group of 20%.

There was no statistically significant difference in the percent of subjects who had a clinically significant improvement in QOL between the treatment and sham groups at the end of the blinded evaluation period.

The Sponsor has also collected data from the open label period, when subjects in both the Treatment and Sham groups received stimulation. There was a statistically significant change in seizure frequency in the Sham group when the first 84 days of stimulation are compared to baseline in seizure frequency; however, the change between the more recent Blinded Evaluation Period and the beginning of the Open Label Phase was not statistically significant. Note that there are several points that confound the interpretation of the open label phase. In particular, during the open label phase all subjects were aware that they were receiving stimulation, changes in

antiepileptic medications were permitted, and there are missing data (43 subjects discontinued treatment, 3 of whom were lost to follow-up, and 23 of whom withdrew electively). The percent of all open label subjects who achieved a clinically significant improvement in QOL did not increase during the open label phase.

9.7.3. Benefit Risk Analysis

Based on the primary safety endpoints, the safety data demonstrate that the level of serious adverse events is not worse than those for deep brain stimulator implantation. These procedures all carry risks considerably in excess of those expected in a comparable medically treated population. Approximately 20% of patients would be expected to experience a serious adverse event related to implantation and associated medical procedures within the 12 weeks following implantation. The effectiveness data demonstrate a difference in mean seizure frequencies between the Treatment and the Sham groups. However, the confidence interval around this difference depends on the analysis model used, and it is subject to a number of other uncertainties. The apparent benefit does not correlate with the difference of 2% in responder rate between Treatment and Sham was not statistically significant. Similarly, other secondary endpoints were small and not statistically significant. The Panel will be asked to consider the safety and effectiveness that have been demonstrated in these clinical studies and recommend whether the benefits outweigh the risks.

10. Statistical Methodology

10.1. Comparison of Pre-specified and Final Model

10.1.1. Pre-specified Model

The initially pre-specified model was:

$$E\left[\ln\left(Y\right)\right] = \beta_0 + \beta_1 Time + \beta_2 Group * Time$$

where the dependent variable, Y, is *daily* seizure counts, and the model is a GEE using a Poisson distribution, a log link, estimation of the "scale" parameter to account for overdispersion, unadjusted for the clinical covariates used in the randomization.

10.1.2. Final model

The final model selected by the sponsor was:

$$E\left[\ln\left(Y\right)\right] - \ln(Days) = \beta_0 + \beta_1 Time + \beta_2 Group * Time + \left\{\beta_{Zone} Zone + \beta_{NFoci} NFoci + \beta_{Surg} Surg\right\}$$

where the dependent variable, Y, is *monthly* seizure counts, and the model is a GEE using a negative binomial distribution, a log link, estimation of the "scale" parameter to account for overdispersion, adjusted for the clinical covariates used in the randomization. The additional terms in the model are: ln(Days), an offset to account for the differing duration of follow-up for each subject; and the clinical covariates Zone (mesial or non-mesial seizure focus origin), NFoci (number of seizure foci), and Surg (previous surgery for epilepsy).

The differences between the two models are presented in the table below.

Table 59. Comparison of pre-specified and post hoc GEE analysis models

Model form option	Pre-defined model	Final model
Statistical distribution of response	Over-dispersed Poisson	Negative binomial
Method of standard error estimation	Not explicitly specified (model-based used)	Model-based
Time scale	Daily seizure count	Monthly seizure count
Adjusted for clinical covariates used in randomization?	No	Yes

For both models, the null and alternative hypotheses are to test the treatment group by time interaction term:

$H_0 : \beta_2 = 0$

$H_A : \beta_2 \neq 0$

The treatment group by time interaction term assesses whether the change in seizure frequency over time is the same for the Treatment and Sham treated subjects ($\beta 2=0$) or different ($\beta 2 \neq 0$). A positive value would indicate that Treatment stimulation increases seizures relative to Sham stimulation, while a negative value would indicate that Treatment stimulation decreases seizures relative to Sham stimulation.

Neither the description of the pre-specified model, nor the final model, included a main effect for treatment. The sponsor justified this omission by arguing that the randomization would ensure that the treatment and control cohorts were not statistically significant. However, the sponsor presented the results of the analysis including a main effect of treatment, which are similar to the model without the main effect of treatment (results not shown in this Executive Summary).

In addition, neither the protocol nor the statistical analysis plan (SAP) discussed which standard error estimate would be used: the empirical or the model-based. In subsequent discussion with the review team, the sponsor has subsequently argued that the use of the model-based standard errors was implied by the estimation of the over-dispersion parameter in the pre-specified model, as the model-based standard errors are adjusted for this term while the empirical standard errors are not.

10.2. Robustness of primary effectiveness outcome to alternative analysis models

Additional GEE analysis models were conducted by CDRH to serve as sensitivity analyses to explore how robust the treatment effect observed in the sponsor's post hoc model are to the particular combination of assumptions of that sponsor's post hoc model.

10.3. Appropriateness of alternative GEE models

The sponsor has argued that several of these alternative models (e.g. those using the Poisson distribution or unadjusted for the clinical covariates) are not appropriate and therefore should not be expected to provide reliable inference for this dataset. They argue that the treatment effect is robust across several alternative appropriate models; e.g. using the unstructured working correlation structure

(excluding subjects with more than 9.5 seizures per day), a model including an effect for clinical center, a model including a main effect of treatment, and models containing various permutations of covariates.

The sponsor noted that the pre-specified primary effectiveness analysis model (GEE using Poisson distribution, on daily seizure counts, unadjusted for the clinical covariates in the randomization) was not a good fit to the data. As a result, the sponsor modified the primary effectiveness analysis model (GEE using negative binomial distribution, on monthly seizure counts, adjusting for the clinical covariates in the randomization).

While CDRH agreed with the sponsor that the pre-specified model was not a good fit to the data, and that the post hoc model is a more efficient model than other GEE models examined, the purpose of the Forest plot provided in Figure 5 (§6.2.22.2.6) was to assess via a sensitivity analysis how dependent the estimated treatment effect and statistical significance the results from the post hoc GEE model were upon the particular model settings used in the post hoc model. The results suggest that, while the estimated treatment effect is consistent across multiple GEE models, statistical significance is dependent upon particular combinations of model settings.

10.4. Statistical Conclusion

The originally proposed primary endpoint was mean reduction in the number of seizures between Sham and Treatment groups using a GEE model with a given set of assumptions. The sponsor and CDRH agree that the originally pre-specified analysis model was not a good fit. The revised model proposed by the sponsor, relying upon different assumptions, is not incorrect; it is simply not the sole appropriate model which could have been applied. It is therefore of interest to examine how sensitive the estimated treatment effect is to the particular assumptions of the revised analysis. While the sponsor has justified the choices they have made from the originally pre-specified analysis model to the revised post hoc model, several issues remain. Firstly, many of these choices could have been pre-specified, but were not (e.g. grouping by month, adjusting for the clinical covariates used in the randomization, use of negative binomial distribution rather than the overdispersed Poisson distribution); this complicates matters in the context of a *post hoc* analysis conducted after the data had been unblinded.

In addition, there are several sources of uncertainty present in this dataset:

- Lack of statistical significance in the secondary outcomes
  While the trial was not explicitly powered to demonstrate statistical significance on the secondary outcomes (with the exception of responder rate, which formed the basis of the trial's sample size calculation) the lack of statistical significance on the secondary outcomes may be due to there being no treatment effect, or the trial being underpowered to detect a difference of the magnitude seen in the trial.

- Alternative GEE models
  While the sponsor has provided justifications for the changes from the pre-specified and final model, these provide support that the final model is appropriate but not necessarily that it is the only appropriate model for this dataset. The observation that not all of the alternative GEE models

are statistically significant raises concerns regarding how robust the observed treatment effect is to alternative model assumptions.

- Differential treatment effect by baseline seizure frequency
  In order to assess an underlying assumption of the GEE model (that the observed treatment effect is homogenous across baseline seizure frequency) the post hoc GEE model was replicated by examining the results separately by 4 categories of baseline seizure frequency. The results suggest that the observed treatment effect is not consistent, but rather mainly limited to those subjects with the highest seizure frequency at baseline.

- Influence of 2 highly influential Sham-treated subjects on the overall estimated treatment effect
  The plot of the mean response by treatment group suggests that the Treatment group experiences a reduction in seizures over time, while the Sham treated group shows a transient improvement followed by a gradual attenuation to baseline. However, this response appears to be driven by 2 Sham-treated subjects who had a very high seizure frequency at baseline and actually worsened by the end of the BEP, unlike the majority of Sham-treated subjects who improved over time. When the post hoc GEE analysis model is repeated excluding these 2 subjects, the observed treatment effect is reduced and the mean in the Sham-treated cohort largely mirrors the mean in the Treatment cohort.

11. Post-Approval Studies

NOTE TO PANELISTS: FDA's inclusion of a section/discussion on a Post-Approval study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA device. The presence of post-approval study plans or commitments does not in any way alter the requirements for pre-market approval, and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies should the Panel find the device approvable following its discussion and deliberations of the premarket data.

The FDA review team has made the recommendation that if the NeuroPace® RNS® System (Responsive Neuro-stimulator System) is approved, a post-approval study (PAS) or studies should be required as a condition of approval for this first-of-a-kind device. Through premarket review of the PMA, FDA has identified the following postmarket concerns and recommends that a PAS be conducted to assess the following:

- To collect safety data on recipients of the RNS® System who are being treated by physicians, newly trained on implantation and management of the RNS® System;
- To gather additional patient years of data to contribute to the estimate of the rate of sudden unexplained death in epilepsy (SUDEP).

The sponsor has two PAS protocol proposals:

1. Extended follow-up of premarket subjects: Long Term Treatment (LTT) study. Proposals agreed-on, 2005.
2. New Enrollment Study, proposal dated April 20, 2012.

An overview of the proposed PAS protocols is provided below. Outstanding issues that need to be addressed are included in the assessment following the proposals overview.

11.1. Overview of Proposed Post-Approval Studies

11.1.1. Extended Follow-up of Premarket Subjects: Long Term Treatment Study

Post-Approval Study Questions
There are no postmarket study questions stated in the protocols.

Study Design Description and Hypotheses
The applicant is proposing an extended follow-up of IDE G0309126 studies: the Long Term Treatment (LTT) study.

It is an open label multi-center prospective clinical study designed to assess the safety and to evaluate the long-term effectiveness of the RNS™ System for up to 7 years following a subject's completion of either the RNS™ System Feasibility or the Pivotal Clinical Investigation. All subjects who have completed the 2 years of follow-up in the RNS™ System Feasibility or Pivotal Clinical Investigation are potential candidates for the LTT study (see figure below).

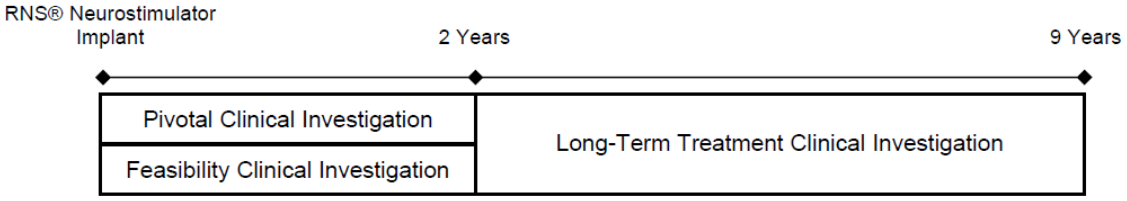


Figure 19. RNS® System Long-Term Treatment Clinical Investigation – Trial Flow and Periods

Study Population
The 7-year follow-up will evaluate the long-term performance of the RNS™ System as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications. Subjects were eligible to enroll into the LTT study if they had completed either the Feasibility or Pivotal studies, had the RNS™ System implanted, had elected to continue to receive responsive stimulation, and were able to attend scheduled appointments for the study. They were not eligible if they had an active psychiatric or mental illness that made it inadvisable for the subject to continue to receive responsive stimulation or if the subject had been diagnosed with psychogenic or non-epileptic seizures, or primarily generalized seizures during the Feasibility or Pivotal studies.

Data Collection (Endpoints)
Subject follow-up includes: office appointments every 6 months and quality of life assessments at yearly appointments. Mortality and adverse events, as defined in the investigational plan, will continue to be collected throughout the LTT study. At each protocol-specified follow-up office appointment, a neurological examination, medication review, vital sign review, assessment of adverse events, review of seizures, and quality of life (QOLIE-89) assessments will be conducted as required by specific protocol time points. Normal monitoring and auditing procedures per NeuroPace practices will be employed.

Long-term safety and effectiveness endpoint analyses as described in detail in the LTT study investigational plan will be submitted to the FDA after completion of the LTT study. These analyses include the following:

Effectiveness
- The primary effectiveness analysis is the average percentage change in the mean frequency of total disabling seizures for each 6-month interval beginning 6 months after implantation of the RNS™ System relative to pre-implant baseline will be reported. Data from the Feasibility, Pivotal, and LTT studies will be included in the analysis.
- Secondary outcome analyses will include the following:
    - Responder Rate - Proportion of subjects with greater than or equal to 50% reduction in total disabling seizures compared to pre-implant baseline
    - Quality of Life - QOLIE-89 scores collected at each year of follow-up after implantation of the RNS™ System compared to the QOLIE-89 at pre-implant baseline

Safety
- The primary safety analysis is the Serious Adverse Event (SAE) rate.
The SAE rate is defined as the proportion of subjects having a serious adverse event.
- SUDEP Rate: Information will be combined from the three RNS™ System Clinical Investigations in epilepsy (Pivotal, Feasibility, and Long-Term Treatment) to collect approximately 1500 patient years of data in order to provide a confident estimate of the rate of Sudden Unexplained Death in Epilepsy (SUDEP). The outcome variable is death classified as possible, probable or definite SUDEP by the SUDEP Analysis Committee occurring in patients programmed to receive stimulation divided by the total number of stimulation years. Upon completion of the Long-Term Treatment Clinical Investigation it will be possible to estimate with 95% confidence that the true rate of SUDEP does not exceed 9.3/1000 patient stimulation years.
- The secondary safety analysis is the Adverse Event (AE) rate. The AE rate is defined as the proportion of subjects having an adverse event.

Follow-up Visits and Length of Follow-up

Proposed follow-up:
The LTT study: 7-year follow up; office appointments every 6 months and quality of life assessments at yearly appointments.

Enrollment Plan and Follow-up Measures
Measures for handling follow-up are not included in protocols.

Statistical Plan
No statistical plan is included in the protocol.

11.1.2. New Enrollment Study with 1-year Follow-Up

Post-Approval Study Questions
There are no study questions stated in the protocol.

Study Design Description and Hypotheses
This will be a prospective, non-randomized, multicenter Post-Approval Safety Study to collect one year of safety data on recipients of the RNS® System who are being treated by physicians newly trained on implantation and management of the RNS® System. A second objective of this post-approval study is to gather additional patient years of data to contribute to the estimate of the rate of sudden unexplained death in epilepsy (SUDEP). Data obtained from this study and the LTT trial after PMA approval of the RNS® System will be combined with data gathered in the pre-approval studies so that 1500 or more years of implant and stimulation patient years of experience can be gathered to provide for a confident estimate of the rate of SUDEP.

The hypothesis for the primary endpoint is that the total serious adverse event rate (device related and not device related) at one year is not worse than the total SAE rate observed in the first year of the RNS® System Pivotal trial, which was 39% (74/191). The serious adverse event (SAE) rate is defined as the proportion of subjects experiencing one or more serious adverse events.

Study Population

A single group of subjects are enrolled in the open label Post-Approval Safety Study. A second group of subjects, the implanted pivotal study cohort at one year of follow-up, will serve as the comparator group for the primary safety analysis.

Key Inclusion Criteria:
- 18 to 70 years of age.
- Disabling seizures (simple partial motor, complex partial and/or generalized tonic clonic seizures).
- Failed treatment with a minimum of two antiepileptic medications (used in appropriate doses) with adequate monitoring of compliance and the effects of treatment, as determined by the physician investigator.
- Has undergone diagnostic testing as part of his/her standard care that has identified no more than two epileptogenic regions.
- Patient is unlikely to move and agrees to return to the study center for the required number of follow-up visits.

Key Exclusion Criteria:
- Diagnosed with primarily generalized seizures or has been diagnosed with psychogenic or non-epileptic seizures in the preceding 2 years.

- Diagnosed with active psychosis, major depression or suicidality in the preceding 2 years. Subjects with post-ictal psychiatric symptoms are not excluded. The screening version of the Columbia-Suicide Severity Rating Scale will be used to assess suicidality.
- In the opinion of the investigator, subject has a clinically significant or unstable medical condition (including alcohol and/or drug abuse) or a progressive central nervous system disease.
- English is not the primary language spoken.

Sample Size (Patients and Sites)
It is anticipated that as many as 25% of subjects will withdraw from the study during the first year because they no longer wish to participate in study data collection. Therefore, to ensure sufficient data are collected to adequately power the primary endpoint comparison, a minimum of 158 subjects is required. While 158 subjects would provide sufficient power for the primary analysis, additional objectives of the study include gaining experience at a meaningful percentage of Level IV Epilepsy Centers. The study will be conducted at 20 epilepsy centers, with the goal of an average of 10 patients enrolling at each site. Thus, 200 subjects will be enrolled.

Data Collection (Endpoints)

Primary Endpoint
The primary objective is to demonstrate that the total serious adverse event rate (device related and not device related) at one year for patients treated by physicians newly trained in implantation and use of the RNS System is not worse than the total SAE rate observed in the first year of the RNS System Pivotal trial.
The serious adverse event rate is defined as the proportion of subjects experiencing one or more serious adverse events.

Other Endpoints
- Evaluate the rate of the following SAEs of special relevance at 1 year after implantation: implant or incision site infection, intracranial hemorrhage, suicidality, and depression.
- Gather additional patient implant years and stimulation years which, when combined with data from the Feasibility, Pivotal and Long-Term Treatment trials, will provide a more confident estimation of the SUDEP rate.

Follow-up Visits and Length of Follow-up

Proposed follow-up in the New Enrollment Study is 1-year post implant. The following scheme will be applied:

Table 60. Proposed Follow-up Visit Schedule

Procedure	Enrollment	Device Implant	Visit (months post-implant)[1]					
			2 wks	1	2	3	6	12
Visit window in days, based on date of implant			± 5	± 10	± 10	± 28	± 30	± 30
Screening[2]	X							
Inclusion/exclusion criteria	X							
Informed consent	X							
Demographics	X							
Medical, surgical and epilepsy history	X							
Device implant		X						
Neurostimulator monitoring		X			X	X	X	X
Adverse event monitoring		X			X	X	X	X
Patient satisfaction survey						X	X	X
Physician satisfaction survey						X	X	X
QOLIE-31	X							X
Beck Depression Inventory	X					X	X	X
Columbia-Suicide Severity Rating Scale	X					X	X	X

[1] One month= 28 days
[2] Subjects will be screened relative to suicidality prior to enrolling into the active portion of the trial.

Enrollment Plan and Follow-up Measures
Participating sites will be asked to enroll 5-15 patients over a 2.5 year period, with the goal of an average of 10 patients participating at each site. NeuroPace will work with participating centers, and the respective IRBs, to generate local advertising modalities including web postings at the clinical institution and local radio and others news media outlets. Information on the study will be posted on the primary NeuroPace website as well as on clinicaltrials.gov.

In order to minimize loss to follow-up, one inclusion criteria will be that the subject is unlikely to move and is willing and able to return to the study center for follow-up visits. Subjects will be reminded of follow-up visits by phone, text, email and, if available, social media sites. In addition, contact information for 4 family members and/or friends will be requested from the subject so that these individuals can be contacted regarding the subject's follow-up appointments. To keep the study "top-of-mind", the subject will receive birthday and holiday cards from the study coordinators. Subjects will receive reasonable reimbursement for travel expenses and for time missed from work.

Statistical Plan
The overall serious adverse event (SAE) rate at one year will be calculated as the number of subjects who experienced one or more SAEs (device related or not) during the first year following implant, divided by the number of subjects implanted during the study. The corresponding success rate at one year – that is, the percentage of subjects who did not have an SAE during the year divided by the number of subjects implanted during the study – will be used in testing the primary study endpoint.

For the additional study endpoints, both the percentage of subjects with SAEs and the number of SAEs reported over time (event rate) at one year post-implant will be calculated for adverse events of special relevance: implant or incision site infection, intracranial hemorrhage, suicidality, and depression. The percentage of subjects will be calculated as the number of subjects experiencing one or more of that type of SAE divided by the number of subjects implanted. The event rate will

be calculated as the number of SAEs of that type reported during the first year post-implant divided by the total number of patient implant years of follow-up subjects during the study.

Percentage of subjects with SAEs and SAE event rates at one year post-implant will be presented as observed in this study and as observed in the RNS System Pivotal Clinical Investigation. Percentage rates will be presented with two-sided 95% confidence intervals estimated using the Score Interval [also known as the Wilson Interval (Zhou et al., 2008)]. Event rates will be presented with two-sided 95% confidence intervals calculated according to patient implant years of follow-up. Since the distribution of rates per number of patient years of follow-up are based on the Poisson distribution, the normal approximation will be applied to the logarithmic transformed rate and the 95% confidence interval will be obtained with the back-transformed result (Miller, 1981; Esteve et al., 1994).

Data regarding SUDEP will be reported similarly to that in the other RNS System Clinical Investigations: Data across all investigations will be pooled and the SUDEP rate will be calculated as the ratio of the number of possible, probable, and definite SUDEP events in subjects programmed to receive stimulation divided by the number of patient stimulation years, with 95% confidence interval calculated according to patient stimulation years of follow-up.

11.2. Assessment of Proposed Postmarket Plan

Extended Follow-up of Premarket Subjects

The extended follow up of the IDE subjects and the LTT study were agreed on with FDA in 2005, which means at the time FDA considered the protocols to suffice.

New Enrollment Study

1. The sponsor has not proposed a newly enrolled comparison group (e.g., best medical therapy), and intends to report total serious adverse event rate as primary study endpoint.

2. In the Pivotal Trial the SUDEP rate was 6.2 deaths per 1000 patient-years for subjects whose Neurostimulators were programmed to provide responsive stimulation and 9.2 deaths per 1000 patient-years in the comparator group. This endpoint will be collected in the New Enrollment Study.

3. The applicant did not propose any subgroup analysis. However it could be of clinical interest to understand whether effectiveness varies according to patient variables such as: various sites of seizure onset; failed VNS therapy; prior ablation/resection procedures.

4. 1-year follow up is proposed, while FDA recommends a 10-year follow up. A longer duration of follow up is usually necessary to estimate the long term safety of the implanted device.

5. A loss to follow up of 25% during the first year is expected in the proposed protocol. Such high loss to follow-up is outside usual standards and prone to provide biased results.

6. The company is proposing to use 39% as the expected rate for Serious Adverse Events (SAE, classified as either device-related or not device-related) in the 1-year follow-up New Enrollment

Study. A rate of 39% expected for SAE among patients implanted with the device is high from a safety perspective.

7. Effectiveness data are not planned to be systematically collected during the new enrollment study. Given that the device is a permanent implant, it is important to monitor long-term effectiveness.

Should the Panel find the device approvable following its discussion and deliberations of the premarket data they will be asked to comment on potential post-approval studies.

12. Appendix I - Tables

Table 61. Clinical Assessments Performed during the Pivotal Study**.**

	Initial	Week			Implant	Weeks Post Implant																					
	Visit	4	8	12	Procedure	2	4	5	6	7	8	12	16	20	24	28	32	36	40	44	48	52	56	68	80	92	104
Assessment Protocol																											
Source Documents																											
Adverse Event Clinical Note		when applicable					when applicable																				
Conclusion-Withdrawal Clinical Note		when applicable					when applicable																				
Consent Form	X																										
Spanish Participation Confirmation Clinical Note[4]	X																										
Eligibility Confirmation Clinical Note				X																							
History & Physical Dictation (Medical Record)	X																										
Inclusion/Exclusion Criteria Clinical Note	X																										
Initial Office Appointment Clinical Note	X																										
Medical History Clinical Note	X																										
Medication Log Clinical Note		X	X	X			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mood Surveys[1]	X													X									X		X		X
My Seizures Table Clinical Note[2]	X	when applicable					when applicable																				
Neuropsychological Evaluation Report[3]				X										X									X				X
Neuropsychological Evaluation Testing Forms[3]				X										X									X				X
Office Appointment - Assessment Clinical Note				X			X				X	X	X	X	X	X	X			X			X	X	X	X	X
Seizure Diary		X	X	X			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Seizure Report Clinical Note		X	X	X			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone Appointment Clinical Note		X	X															X	X		X	X					
Therapy Assessment Clinical Note														X													
eCRFs																											
Adverse Event		when applicable					when applicable																				
Conclusion-Withdrawal		when applicable					when applicable																				
Consent Information	X																										
Eligibility Confirmation				X																							

	Initial	Week			Implant	Weeks Post Implant																					
	Visit	4	8	12	Procedure	2	4	5	6	7	8	12	16	20	24	28	32	36	40	44	48	52	56	68	80	92	104
Inclusion/Exclusion Criteria	X																										
Initial Office Appointment	X																										
Medical History	X																										
Medication Log		X	X	X			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mood Surveys[1]	X													X									X		X		X
My Seizures Table[2]	X	when applicable					when applicable																				
Neuropsychological Evaluation[3]				X										X									X				X
Office Appointment - Assessment				X			X				X	X	X	X	X	X	X			X			X	X	X	X	X
Seizure Report		X	X	X			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone Appointment		X	X															X	X		X	X					
Therapy Assessment														X													
Treatment Protocol																											
Source Documents																											
Adverse Event Clinical Note					when applicable																						
Breaking the Blind Clinical Note						when applicable																					
Hospital Discharge Summary Dictation (Medical Record)					X	when applicable																					
Implant Procedure Summary Dictation (Medical Record)					X	when applicable																					
RNS® System Investigational Procedure Form					X	when applicable																					
Office Appointment - Treatment Clinical Note						X	X	X	X	X	X	X	X	X	X	X	X			X			X	X	X	X	X
Surgical Procedure Clinical Note					X	when applicable																					
X-ray of Implanted RNS® System					X	when applicable																					
eCRFs																											
Adverse Event					when applicable																						
Breaking the Blind						when applicable																					
Office Appointment - Treatment						X	X	X	X	X	X	X	X	X	X	X	X			X			X	X	X	X	X
Surgical Procedure					X	when applicable																					

[1] BDI, QOLIE-89, CES-D, POMS (QOLIE-31 and the POMS Brief instead of the QOLIE-89 and POMS for Spanish speaking subjects)

[2] After the initial office visit, the My Seizure Table Clinical Note and eCRF should only be updated if the subject experiences a change in seizures

[3] The initial Neuropsychological Evaluation Battery must be administered between the date of qualification and implant surgery

[4] Only required for Spanish-speaking subjects

Note: Baseline appointments continue to follow the same schedule until date of qualification for implant or until subject is withdrawn.

Table 62. Pivotal Safety – Neuropsychological Assessments at End of Blinded Evaluation Period Relative to Baseline (Treatment and Sham Groups) Analysis includes subjects (N) with assessments available at both Baseline and at the end of the Blinded Evaluation Period (20 weeks).[2]

Neuropsychological Variable	Summary Score								
	Treatment				Sham				Difference in Change from Baseline Tx and Sham p-value[1]
	N	Baseline (mean ± sd)	End of Blinded Evaluation) (mean ± sd)	Change from Baseline (mean ± sd)	N	Baseline (mean ± sd)	End of Blinded Evaluation (mean ± sd)	Change from Baseline (mean ± sd)	
Visual Motor Speed									
Trailmaking – Part A**	91	37.86 ± 18.94	38.73 ± 20.87	0.87 ± 14.61	86	46.34 ± 33.25	45.97 ± 32.86	-0.37 ± 14.97	0.578
Trailmaking – Part B**	90	110.66 ± 75.55	104.63 ± 69.39	-6.02 ± 52.72	85	126..42 ± 83.33	120.36 ± 83.74	-6.06 ± 33.49	0.996
Motor Speed / Dexterity									
Grooved Pegboard – Dominant**	89	89.96 ± 32.04	88.72 ± 32.94	-1.24 ± 14.95	79	97.54 ± 52.00	95.35 ± 48.30	-2.19 ± 26.60	0.746
Grooved Pegboard – Nondominant**	88	99.93 ± 37.69	98.05 ± 33.19	-1.89 ± 18.81	75	113.92 ± 60.10	115.24 ± 64.43	1.32 ± 27.31	0.378
Auditory Attention									
WAIS-III Digit Span	90	7.93 ± 2.88	7.72 ± 2.76	-0.21 ± 1.55	86	7.86 ± 2.88	7.95 ± 3.02	0.09 ± 1.48	0.185
General Verbal Ability									
WAIS-III Information	91	7.64 ± 2.94	7.75 ± 3.07	0.11 ± 1.14	83	7.90 ± 3.09	8.02 ± 3.10	0.12 ± 1.17	0.952
General Visuospatial Ability									
WAIS-III Block Design	90	8.83 ± 2.92	8.80 ± 3.30	-0.03 ± 2.06	84	8.40 ± 2.70	8.71 ± 3.08	0.31 ± 1.62	0.227
Verbal Memory									
RAVLT – I-V (Sum Across Trials)	86	41.19 ± 11.07	39.24 ± 11.84	-1.94 ± 9.20	84	41.10 ± 11.40	40.88 ± 11.81	-0.21 ± 10.01	0.243
RAVLT – VII (Delayed Recall)	86	6.47 ± 3.98	6.36 ± 3.73	-0.10 ± 2.75	84	6.75 ± 4.21	6.76 ± 4.20	0.01 ± 2.33	0.766
RAVLT – Recognition Memory	86	12.60 ± 2.39	12.40 ± 2.99	-0.21 ± 2.69	83	12.07 ± 3.07	12.30 ± 3.28	0.23 ± 3.12	0.329
Visuospatial Memory									
BVMT-R – Total Recall	90	17.33 ± 7.57	19.28 ± 8.41	1.94 ± 6.16	85	16.62 ± 9.10	18.62 ± 8.78	2.00 ± 5.95	0.952
BVMT-R – Delayed Recall	87	6.56 ± 3.44	6.79 ± 3.75	0.24 ± 2.75	85	6.28 ± 3.85	6.60 ± 3.93	0.32 ± 2.26	0.832
BVMT-R – Recognition Discrimination Index	88	4.88 ± 1.59	5.01 ± 1.58	0.14 ± 1.42	83	4.95 ± 1.20	4.88 ± 1.40	-0.07 ± 1.24	0.309
Language									
BNT - Spontaneous with semantic cue	90	41.47 ± 12.54	42.17 ± 13.08	0.70 ± 4.37	84	41.99 ± 12.54	43.35 ± 12.80	1.36 ± 3.89	0.297
D-KEFS Verbal Fluency Test – Condition 1: Letter Fluency	83	6.33 ± 3.58	6.27 ± 3.48	-0.06 ± 1.69	77	7.06 ± 3.94	7.60 ± 4.44	0.53 ± 2.32	0.065
Design Fluency									
D-KEFS Design Fluency – Total	89	8.42 ± 3.15	8.91 ± 3.71	0.49 ± 2.32	80	8.16 ± 3.31	8.56 ± 3.09	0.40 ± 2.40	0.795

Neuropsychological Variable	Summary Score								
	Treatment				Sham				Difference in Change from Baseline Tx and Sham p-value[1]
	N	Baseline (mean ± sd)	End of Blinded Evaluation) (mean ± sd)	Change from Baseline (mean ± sd)	N	Baseline (mean ± sd)	End of Blinded Evaluation (mean ± sd)	Change from Baseline (mean ± sd)	
Composite									

[1] Statistical significance of the between-group difference in change in score (at 20 weeks relative to pre-implant) between Treatment and Sham groups per two-sample t-test.

[2] Appendix 15.3.2 (of the Pivotal clinical study report provided in Appendix 10.14.3.2 of this PMA application) provides details regarding assessment availability

** Variables for which lower mean values indicate better performance.

Abbreviations: WAIS-III = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; BVMT-R = Brief Visuospatial Memory Test-Revised; BNT = Boston Naming Test (60 item); D-KEFS = Delis-Kaplan Executive Function System.

Data as of June 4, 2011

Table 63. Pivotal Safety – Neuropsychological Functioning at 56 and 104 Weeks During the Open Label Relative to Baseline (All Subjects Combined) Analysis includes subjects (N) with assessments available at both (Open Label and Baseline) time points.

Neuropsychological Variable	56 Weeks Post-Implant					104 Weeks Post-Implant				
	N	Baseline (Mean ± SD)	56 Weeks (Mean ± SD)	Change from Baseline (Mean ± SD)	Change from Baseline p-value[1]	N	Baseline (Mean ± SD)	104 Weeks (Mean ± SD)	Change from Baseline (Mean ± SD)	Change from Baseline p-value[1]
Visual Motor Speed										
Trailmaking – Part A**	157	42.57 ± 28.01	40.98 ± 28.25	-1.59 ± 15.29	0.196	154	40.79 ± 26.63	39.32 ± 24.29	-1.47 ± 18.75	0.333
Trailmaking – Part B**	154	118.07 ± 79.68	110.79 ± 74.73	-7.28 ± 43.92	0.041	150	113.97 ± 74.53	108.02 ± 73.84	-5.95 ± 46.73	0.121
Motor Speed / Dexterity										
Grooved Pegboard – Dominant**	151	93.48 ± 41.74	91.01 ± 40.67	-2.47 ± 20.68	0.145	147	92.40 ± 41.29	90.40 ± 41.37	-2.00 ± 22.82	0.289
Grooved Pegboard – Non-Dominant**	145	106.43 ± 50.26	105.75 ± 52.15	-0.68 ± 28.72	0.776	143	103.36 ± 46.51	103.14 ± 47.35	-0.22 ± 30.44	0.932
Auditory Attention										
WAIS-III Digit Span	156	7.99 ± 2.91	7.88 ± 2.90	-0.10 ± 2.01	0.526	152	7.96 ± 2.69	8.00 ± 3.03	0.04 ± 1.74	0.781
General Verbal Ability										
WAIS-III Information	156	7.80 ± 2.93	7.99 ± 3.11	0.19 ± 1.27	0.069	153	7.78 ± 3.06	8.09 ± 3.30	0.31 ± 1.32	0.004
General Visuospatial Ability										
WAIS-III Block Design	156	8.53 ± 2.77	8.97 ± 3.26	0.44 ± 1.88	0.004	152	8.72 ± 2.79	9.29 ± 3.10	0.57 ± 2.02	0.001
Verbal Memory										
RAVLT – I-V (Sum Across Trials)	145	41.06 ± 11.12	42.86 ± 11.88	1.80 ± 7.99	0.008	145	40.92 ± 11.28	41.87 ± 11.83	0.95 ± 8.81	0.196
RAVLT – VII (Delayed	144	6.56 ± 4.08	6.99 ± 4.51	0.42 ± 2.54	0.047	147	6.75 ± 4.10	6.96 ± 4.14	0.21 ± 2.71	0.346

Neuropsychological Variable	56 Weeks Post-Implant					104 Weeks Post-Implant				
	N	Baseline (Mean ± SD)	56 Weeks (Mean ± SD)	Change from Baseline (Mean ± SD)	Change from Baseline p-value[1]	N	Baseline (Mean ± SD)	104 Weeks (Mean ± SD)	Change from Baseline (Mean ± SD)	Change from Baseline p-value[1]
Recall)										
RAVLT – Recognition Memory	144	12.31 ± 2.85	12.47 ± 2.97	0.17 ± 2.44	0.413	145	12.38 ± 2.72	12.60 ± 2.95	0.22 ± 2.48	0.286
Visuospatial Memory										
BVMT-R – Total Recall	153	17.28 ± 8.20	18.10 ± 8.54	0.82 ± 6.06	0.095	149	17.64 ± 8.03	18.54 ± 8.12	0.90 ± 5.30	0.040
BVMT-R – Delayed Recall	151	6.44 ± 3.62	6.50 ± 3.61	0.06 ± 2.69	0.797	147	6.58 ± 3.53	6.51 ± 3.49	-0.07 ± 2.17	0.704
BVMT-R – Recognition Discrimination Index	149	4.99 ± 1.29	5.07 ± 1.46	0.08 ± 1.29	0.446	145	5.04 ± 1.32	4.95 ± 1.46	-0.09 ± 1.44	0.454
Language										
BNT - Spontaneous with semantic cue	154	42.18 ± 12.09	43.44 ± 12.41	1.25 ± 4.00	<0.001	149	42.36 ± 12.02	43.64 ± 13.09	1.28 ± 4.04	<0.001
D-KEFS Verbal Fluency Test – Condition 1: Letter Fluency	136	6.58 ± 3.73	6.53 ± 3.38	-0.05 ± 2.13	0.778	138	6.99 ± 3.82	7.12 ± 3.56	0.13 ± 2.31	0.508
Design Fluency										
D-KEFS Design Fluency – Total Composite	150	8.35 ± 3.13	9.65 ± 4.14	1.29 ± 3.14	<0.001	146	8.56 ± 2.97	9.79 ± 3.22	1.23 ± 2.43	<0.001

[1] Statistical significance of the change from the Baseline score per the paired t-test.

[**] Variables for which lower mean values indicate better performance.

Abbreviations: WAIS-III = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; BVMT-R = Brief Visuospatial Memory Test- Revised; BNT = Boston Naming Test (60 item); D-KEFS = Delis-Kaplan Executive Function System.

Data as of May 12, 2011.

13. Appendix II: Statistical background on GEE models

The clinical trial conducted by the sponsor for the RNS® System utilized a repeated measures design; as such, the repeated observations on the same subject over time are correlated, and this correlation must be accounted for in the analysis to draw correct inferences. Generalized Estimating Equation (GEE) models can accommodate this type of data, but require specification of several model options to fit. These modeling options are described in turn in the following sections.

Generalized estimating equations (GEE) were originally developed by Liang and Zeger (1986). The initial uses were for analyzing correlated binary data, but were later developed to analyze for count data. These models can be used to analyze longitudinal count data, such as arises from monitoring the subjects with epilepsy and counting the number of seizures they experience within a given time-period.

GEE models require specification of three model options: which working correlation structure to use, which statistical distribution to use, and which method of estimating the standard error to use (Ballinger, 2004). Once these three options have been selected, the GEE model starts with an initial value for the parameter effects, then solves for the values of the covariance matrix (the matrix of values that determines the variance for the parameter effects). This covariance matrix is then used to update the estimated parameter effects, which are then used to update the estimated covariance matrix. The model continues this iterative numerical process until the values stabilize (e.g. the update changes the values by less than $1*10^{-7}$) to determine the most likely values for the parameters. The parameter estimates and covariance matrix are then used to estimate the effect of treatment (for the NeuroPace trial, this is expressed in terms of a percent change from baseline in seizure frequency).

A.1 Working correlation structure

Before the model can begin to iteratively solve for the parameter estimates, a set of initial values must be selected and input. To select initial values for the variance parameters, a working correlation structure must be specified; this working correlation serves as a scaffold for the variance of the GEE model. The working correlation structure establishes what the investigator believes to be the most likely relationship among the correlated outcomes – in the NeuroPace trial, this corresponds to how related the monthly seizure count frequencies within a given subject are. While several correlation structures can be selected, the two most commonly used are unstructured and exchangeable (sometimes called compound symmetrical). The unstructured approach does not assume any structure; however, this approach often requires a large dataset and may not converge with smaller datasets (e.g. in the NeuroPace trial the unstructured approach fails to converge – i.e. does not provide a final parameter estimate). The exchangeable structure assumes that all time-points are equally correlated (e.g. the strength of the correlation between baseline and month 4-5 of the BEP is the same as the strength of the correlation between month 2-3 of the BEP and month 4-5 of the BEP). Other working correlation structures can be used but these are not discussed here. The NeuroPace trial used an exchangeable structure.

A.2 Statistical distribution: over-dispersed Poisson or negative binomial

Count data are typically analyzed using the Poisson distribution; however, count data arising from biological processes often demonstrate substantially more variability than predicted by the Poisson distribution – this is typically referred to as overdispersion (Stokes et al., 2000). Two statistical

distributions are commonly used to analyze overdispersed count data: the over-dispersed Poisson and negative binomial; the over-dispersed Poisson model is a special case of the negative binomial distribution. Both of these models are designed to allow the variance of the data to exceed the mean, which is a restriction imposed by the standard Poisson distribution. There is a substantial statistical literature addressing this issue, summarized below; however, there is not a consensus on the issue. Most investigators suggest that the negative binomial model is an alternative to the over-dispersed Poisson rather than as a definitive replacement.

Examples of literature suggesting the negative binomial as an alternative, rather than the default replacement, include Fleiss *et al.* (2003), the SAS PROC GENMOD help documentation, Littell *et al* (2002), and Fitzmaurice *et al.* (1993).

On the other hand, several authors have suggested the routine use of the negative binomial model in place of the Poisson. Trocóniz *et al*. (2009) discuss four models for analyzing overdispersed count data (with epilepsy trial data as an illustrative example): Poisson, zero-inflated Poisson, negative binomial, and zero-inflated negative binomial. Importantly, however, they did not consider the over-dispersed Poisson approach. They conclude that the negative binomial resulted in the best fit to the data in their example (p 461). Ballinger (2004) (citing Gardner *et al*., 1995) also suggests that the negative binomial model be used for data with high overdispersion. However, Gardner *et al*. (1995) appear to be more moderate in their recommendation for this context. They discuss both the over-dispersed Poisson and the negative binomial distribution as alternatives. They explain the negative binomial model as effectively a random-effects model. In their conclusion, they describe the over-dispersed Poisson and negative binomial approaches as alternatives, without universally suggesting one as superior. They suggest that the choice is dependent upon the underlying goal of the research: they recommend the quasi-likelihood approach "when the researcher is interested primarily in the hypothesis tests about the regression coefficients of the log-linear model," and the negative binomial "when it is important to estimate the probability distribution of an individual count." (p 403).

Conversely, when Stokes *et al.* (2000) discuss overdispersed data, they suggest GEE as an alternative to both approaches. As discussed above in the section about which standard error approach to use, these authors recommend using the Poisson distribution with empirical standard errors.

The sponsor has previously noted that the literature suggesting the over-dispersed Poisson and negative binomial models as equivalent are based upon examples with relatively moderate over-dispersion, which is of limited relevance in the setting of this trial given the larger over-dispersion in their dataset.

A.3 Empirical vs. model-based standard error estimate

Inference in GEE models follows standard procedures, with a 95% confidence interval being calculated based upon the parameter estimate and its estimated variance. However, the estimated variance can be calculated in one of two ways: using model-based estimate or the empirical (sometimes referred to as robust or sandwich estimate). The model-based estimate assumes that the variance component of the GEE model has been correctly specified (i.e. the underlying statistical distribution and the working correlation structure). The empirical estimate uses the model-based estimate but calibrates it by incorporating the variances observed in the data. As a result, if the model is correctly specified the 2 estimates will provide similar conclusions, although the calibration

procedure used by the empirical approach can result in a more conservative (i.e. less powerful) estimate than the model-based estimate. If the model is not correctly specified then the model-based estimate can be significantly inaccurate, while the empirical estimate is less impacted – this trait of the empirical estimate is referred to as consistency.

The choice of which estimation approach to use has been discussed extensively in the statistical literature. Hardin and Hilbe (2003) argue that the empirical estimate of the variance is "robust to *any* form of within-panel correlation," and thus it helps to protect against "misspecification of the within-panel correlation." A similar point is made by Fleiss *et al.* (2003), who state that the "sandwich estimate enables us to draw correct inferences even when the correlation structure is mis-specified". Agresti (2002) also appears to recommend the empirical estimate, stating that "the naïve standard errors based on the independent assumption are updated using the information the data provide about the actual dependence structure to yield more appropriate (*robust*) standard errors," and that "the purpose of the sandwich estimator is to use the data's empirical evidence about covariance to adjust the standard errors in case the true covariance differs substantially from the working guess." Breslow (1990) suggests the use of the empirical covariance matrix if there is concern that the specification may not be correct. He concludes "In spite of the greater precision of the scaled Poisson analysis, I recommend the empirical variances and especially the empirical score test in overdispersed Poisson regression problems where the true mean/variance relationship is not well established by prior experience and the sample size is sufficiently large". Hosmer and Lemeshow (2000), when describing the GEE, mention that some software packages will also calculate the model-based estimator, but conclude that "unless there is strong evidence from other studies or clinical considerations that the working correlation structure is correct, one should use the [sandwich estimator]". Littell *et al.* (2002) state that "inference with GEEs typically replace the model-based variance by the robust, or empirical estimate. Provided that the sample size is adequate, the empirical estimate has the advantage that when it is used, correct inference does not depend on getting the working correlation matrix right." However, they do caution that, "with very small samples, however, test statistics computed with the empirical estimate can be inflated, sometimes wildly."

Stokes *et al.* (2000) state that PROC GENMOD provides both the empirical and model-based estimates, and that "if these matrices are very similar, you may have some confidence that you have correctly specified the correlation structure and the estimates are relatively efficient. However, recall that, even if you have mis-specified the correlation structure, both the parameter estimates and their empirical standard errors are consistent, provided that the specification is correct for the explanatory variables". When Stokes *et al.* (2000) discuss over-dispersed data, they state that an alternative to using the negative binomial distribution or over-dispersed Poisson analysis is to use a GEE approach. They note that the empirical covariance matrix is robust to mis-specification, and that the over-dispersion can be considered a source of mis-specification of the variance structure. After examining an example dataset, they conclude that there is evidence of overdispersion, and thus "the model-based estimates of standard errors may not be appropriate and therefore any inference is questionable…The next step is to account for this overdispersion with the GEE-generated robust covariances…Using the GEE method, you are using a measure of variability based on the data to do the adjustment, rather than a single parameter (scaling factor) applied to the covariance matrix. With the GEE method, using the robust variances, you are providing a measure of variability for each parameter you estimate together with the corresponding covariances, all based on your data. In many situations, this strategy may be a practical approach to handling overdispersion." Importantly, the example used for

illustration has evidence of over-dispersion in a standard Poisson regression, so they then apply a GEE model which retains the Poisson distribution and relies upon the empirical, rather than the model-based, variances. It is also worth noting that they do not include an over-dispersion scale parameter to adjust the model-based standard error, relying upon the GEE model and empirical standard error to account for the overdispersion.

The sponsor states that, in the models they have identified as appropriate, the choice of standard error does not alter the statistical significance of the estimated treatment effect. They also cite a comment by Drum and McCullagh (1993) to an article by Fitzmaurice, Laird & Rotnitzky (1993). Their criticism is that "consistency, even when the assumed variance function is incorrect, is the sole property used to justify the adjective robust…The overall conclusion that we draw from these and other examples is that the empirical sandwich estimator can be a useful tool in applied work if all sample sizes are sufficiently large. It is not a panacea, nor does it supersede the model-based estimate… For these reasons, unless there is good reason to believe that the assumed variance function is substantially incorrect, the model-based estimator seems to be preferable in applied work, particularly where small samples are involved. Ideally, one should compute both estimates and aim to understand any differences that occur."

A.4 Time period

The original model analyzed daily seizure counts; the sponsor's revised post hoc model grouped seizure counts by month. This choice was justified by citing the extreme variability in day-to-day response, as well as pointing out that there are approximately 168 days per subject (making modeling difficult). They then point to extant literature in the epilepsy field which groups seizure counts by month, as well as an FDA communication to them (9/15/05) which suggested that they group the daily counts into months. At the time, however, the sponsor elected not to group by month, arguing that doing so would discard valuable information relative to analyzing on the daily scale.

The Forest plot provided earlier in the FDA Executive Summary demonstrates that the model predicted treatment effect is fairly consistent regardless of whether the data are analyzed by day or grouped by month. However, grouping by month does have a substantial impact on the variance estimate. As a result, the conclusion from the model is somewhat sensitive to this grouping, and grouping at some other level (e.g. by 2-week period) may yield different results than either the daily or monthly analysis.

A.5 Adjusting for clinical variables used in the randomization

The initial model did not adjust for any clinical variables, although the PMA submission states that "additional models including covariates that potentially influence the endpoint and covariates that were found not to be balanced between the groups were to be included in the model" (P100026, Vol 10, p 158). In justifying the inclusion of covariates, the sponsor cites the Friedman *et al*. clinical trials text, the CDRH guidance document on statistical issues in non-diagnostic medical device trials, and Kernan *et al*. in justifying including these clinical covariates in the model.

The pivotal trial's randomization utilized a minimization approach based on four covariates in the order: center, partial onset mesial temporal origin vs. elsewhere, unifocal vs. bifocal onset zone, and previous therapeutic surgery for epilepsy. The chi-squared approach of Smoak and Lim (2001) was used to assess imbalance as each new subject was randomized; the treatment group resulting in

greater balance was favored in the randomization ratio (i.e. it was still random, not deterministic). The sponsor presented the results of four subset analyses, consisting of the 3 clinical covariates included in the randomization as well as difference in antiepileptic medication/benzodiazepine use.

An interesting point is that the minimization process appears to have come close to failing in at least one respect; there is evidence of an imbalance between Treatment and Sham stimulation groups with regard to the number of seizure foci: 49% (48/97) of Treatment and 62% (58/94) of Sham subjects are classified as bifocal (p=0.089) (Table 64). The sponsor did not present a similar tabulation by clinical center, but the breakdown by center appears to be reasonably balanced.

Table 64. Imbalance between Treatment and Sham stimulation groups with regard to the number of seizure foci

Characteristic	Treatment	Sham	*p*-value
Seizure onset location - mesial temporal lobe only (vs. other)	49% (48/97)	50% (47/94)	0.943
Number of seizure foci - bifocal (vs. unifocal)	49% (48/97)	62% (58/94)	0.089
Prior therapeutic surgery for epilepsy	35% (34/97)	30% (28/94)	0.437

The revised model did not include clinical center, although it was the first variable used in the minimization balance algorithm. However, when the sponsor's revised analysis is re-run with the inclusion of clinical center the results are largely unchanged.

Overall, the statistical literature generally favors including covariates used in the randomization in the analysis; particularly in this case, as the trial used a minimization approach rather than a stratified randomization. In the revised model, both seizure onset zone and number of seizure foci are statistically significant, although prior therapeutic therapy was not. However, two issues are unclear: why clinical center (the first covariate used in the minimization) is not included in the model as well, and why the originally proposed model was not adjusted for these covariates.

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